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Diagnostics of Osteoporosis, Fracture Detection, and Monitoring of Pharmacological Treatments Using Bone Mineral Density Derived from Dual-Energy X-ray Absorptiometry and Quantitative Computed Tomography in Real-World Settings

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LIST OF ABBREVIATIONS

aBMD areal bone mineral density
BMC bone mineral content
BMD bone mineral density
COVID Coronavirus disease
DRKS German Clinical Trials Register
DVO Dachverband Osteologie e.V.
DXA dual-energy X-ray absorptiometry
FRAX Fracture Risk Assessment Tool
IBE Institute for Medical Information, Processing, Biometry, and Epidemiology
ISCD International Society of Clinical Densitometry
PTH parathyroid hormone
QCT quantitative computed tomography
RANK receptor activator of nuclear factor kappa B
RANKL receptor activator of nuclear factor kappa B ligand
RIS Radiology Information System
ROC receiver operating characteristic
ROI region of interest
SPSS Statistical Package for the Social Sciences

Preliminary remark on the use of language: Any gender-specific terms in this document are intended to be inclusive of all individuals, regardless of gender.

LIST OF PUBLICATIONS

PEER-REVIEWED ARTICLES CONSTITUTING THE BASIS OF THIS DISSERTATION

Boehm E, Kraft E, Biebl JT, Wegener B, Stahl R, Feist-Pagenstert I. Quantitative computed tomography has higher sensitivity detecting critical bone mineral density compared to dual-energy X-ray absorptiometry in postmenopausal women and elderly men with osteoporotic fractures: a real-life study. Archives of Orthopaedic and Trauma Surgery. 2024;144(1):179-88. doi: 10.1007/s00402-023-05070-y.

Boehm E, Sauer C, Baur-Melnyk A, Biebl JT, Harada S, Wegener B, Kraft E, Stahl R, Feist-Pagenstert I. Real-life effects of pharmacological osteoporosis treatments on bone mineral density by quantitative computed tomography. Journal of Bone and Mineral Metabolism. 2024;42(6):741-53. doi: 10.1007/s00774-024-01553-z.

ADDITIONAL PUBLICATIONS DERIVED FROM CONFERENCE POSTERS

Harada S, Fuchs S, Boehm E, Weigl M, Mansmann U, Feist-Pagenstert I. World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2024). P1176 UP TO 9.3-YEAR FOLLOW-UP STUDY ON DENOSUMAB FOR OSTEOPENIA AND OSTEOPOROSIS: COMPARISON BETWEEN TRABECULAR AND CORTICAL BONE MINERAL DENSITY IN SPINES MEASURED BY QUANTITATIVE COMPUTED TOMOGRAPHY. Aging Clinical and Experimental Research. 2024;36(1):174. doi: 10.1007/s40520-024-02766-y.

Harada S, Boehm E, Fuchs S, Weigl M, Mansmann U, Feist-Pagenstert I. Osteologie 2024. P18 The effects of Denosumab on vertebral trabecular and cortical bone mineral density measured by Quantitative Computed Tomography. Osteologie. 2024;33(02):125. doi: 10.1055/s-0044-1782081

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Feist-Pagenstert I, Baur-Melnyk A, Kraft E, Wegener B, Böhm E. Osteologie 2022. P4 Densitometrie mittels QCT. Potenzielle Fehlerquellen eines diagnostischen Verfahrens. Osteologie. 2022;31(03):206-207. doi: 10.1055/s-0042-1755862.

Böhm E, Baur-Melnyk A, Kraft E, Wegener B, Feist-Pagenstert I. Osteologie 2022. P5 DXA und QCT. Verfahren der Osteoporosediagnostik unter relevanten Einflussfaktoren. Osteologie. 2022;31(03):207. doi: 10.1055/s-0042-1755863.

1 CONTRIBUTION TO PUBLICATIONS

In November 2020, the promotion commenced with the doctoral thesis author's significant contribution to designing and planning the study titled *Longitudinal Observational Study of Drug Therapy Strategies for Osteoporosis Using Quantitative Computed Tomography*[1], under the guidance of the supervisory committee. The author contributed to submitting the study to the corresponding ethics committee for assessment and drafted the study protocol. The ethics commission voted on the study in April 2021. The author additionally registered the study retrospectively in the German Clinical Trials Register (DRKS) by the Federal Institute for Drugs and Medical Devices in October 2022.

Contribution to the First Scientific Article of this Cumulative Dissertation

The author of this thesis substantially contributed as the first author to the design and conduct of this study, which was published as the initial scientific article of this cumulative doctorate and was supervised by PD Dr. med. Eduard Kraft and Dr. med. Isa Feist-Pagenstert. The first study aimed to determine the sensitivity of dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT)-derived bone mineral density (BMD) in detecting fractures.

The data acquisition was carried out by the thesis author. Data collection was based on a list of potentially suitable patients performed with a database query of the hospital's internal Radiology Information System (RIS) by PD Dr. med. Dr. rer. biol. hum. Dipl. Inf. Robert Stahl. The data collection process included a retrospective review of patient characteristics, as well as anamnestic and diagnostic information, considering the presence of pathologic fractures. Furthermore, the author of this thesis retrospectively evaluated the bone mineral density assessments obtained from DXA and QCT of the selected patients. DXA scans were reviewed and evaluated according to defined criteria in the Department of Radiology at LMU hospital using standard DXA devices (Lunar Prodigy LS, GE Healthcare, Madison, USA; Lunar Prodigy Advanced, GE Healthcare, Madison, USA). QCT scans were conducted using a single source CT with multi-slice technology (SOMATOM Definition Edge, Siemens Healthineers, Forchheim, Germany), and measurements were analyzed by reviewing the scout view to ensure precise positioning and verifying the contours for accurate detection of the region of interest (ROI). Outcomes assessed included the T-score by DXA, and trabecular and cortical spine BMD by QCT. The thesis author created a dataset with the variables to be analyzed and performed the statistical analysis using, among others, Pearson's correlation test, cross-tabulations with chi-square calculation, and ROC analyses, conducted with the Statistical Package for the Social Sciences (SPSS). All findings were interpreted by the thesis author with the valuable support of other authors, especially Dr. med. Isa Feist-Pagenstert, Prof. Dr. Bernd Wegener and Dr. med. Johanna Biebl.

The first research results were initially presented in two poster sessions at the “Osteologie 2022. Baden-Baden” conference organized by the Dachverband Osteologie e.V. (DVO).

The first draft of the manuscript, along with the tables and figures for publication were created by the thesis author. The co-authors critically reviewed and commented on every manuscript version. All co-authors approved the final article. The manuscript was submitted to the journal Archives of Orthopaedic and Trauma Surgery on May 5, 2023, and was published online after the review process on October 10, 2023.

[1] The submission to the corresponding ethics committee and the registration with DRKS were conducted under the German study title “Longitudinale Beobachtung von medikamentösen Therapiestrategien zur Osteoporose mittels quantitativer Computertomographie”

Contribution to the Second Scientific Article of this Cumulative Dissertation

The first author designed and conducted this study, which culminated in publication of the second scientific article of this cumulative doctorate, in collaboration with several co-authors and under the primary supervision of Dr. med. Isa Feist-Pagenstert. The study sought to evaluate the effects of various pharmacotherapies for osteoporosis on BMD of the thoracic and lumbar spine measured by QCT.

The thesis author carried out the data collection. Patients meeting the inclusion criteria were selected from a database query in the Radiology Information System (RIS), conducted by PD Dr. med. Dr. rer. biol. hum. Dipl. Inf. Robert Stahl. Of the overall study population, 51 patients were prospectively recruited by the thesis author. The author generated a collection of patient characteristics and reconstruction of pharmacological osteoporosis treatments. Additionally, the thesis author analyzed the QCT-derived BMD data supervised by Prof. Dr. med. Andrea Baur-Melnyk. QCT scans were obtained using a single source CT with multi-slice technology (SOMATOM, Definition Edge, Siemens Healthineers, Forchheim, Germany), and measurements were analyzed by reviewing the scout view to ensure precise positioning and verifying the contours to accurately detect the ROI. Each BMD was calculated from the vertebrae used. Trabecular and cortical BMD were evaluated. Consistent vertebral bodies were used in all measurements for each patient for course assessment. A dataset including the outcomes of trabecular and cortical BMD by QCT, pharmacological treatments, as well as patient characteristics was created by the author. Statistical analyses, tables, and figures were performed by Christina Sauer from the Institute for Medical Information, Processing, Biometry, and Epidemiology (IBE), LMU Munich. A linear regression model with mixed effects and random intercept was used to consider the complexity of data structure. Additionally, the thesis author performed analyses of fracture events.

The results were interpreted by the thesis author in collaboration with other co-authors, especially Christina Sauer, Prof. Dr. med. Bernd Wegener, Saori Harada and Dr. med. Isa Feist-Pagenstert. The first findings were presented as a poster at the “Osteologie 2023. Salzburg” conference, organized by the DVO.

The first draft of the manuscript was prepared by the thesis author supported by Christina Sauer and Dr. med. Isa Feist-Pagenstert, with all versions thoroughly reviewed and commented by all co-authors. The co-authors approved the final draft for publication. The manuscript was submitted to the Journal of Bone and Mineral Metabolism on May 10, 2024, and was published online on September 17, 2024.

2 INTRODUCTION

The aging population with associated chronic conditions is becoming an increasingly significant health concern with far-reaching implications for healthcare systems. Osteoporosis is a prevalent systemic skeletal disease characterized by decreased bone mass and impaired bone tissue quality, resulting in increased fragility and an elevated fracture risk [1]. In clinical practice, the primary forms of bone loss most observed are postmenopausal and age-related osteoporosis, with fractures representing the major clinical manifestation [2]. The lifetime risk of osteoporotic fractures from the age of 50 onward can be classified as very high and amounts to about 33% for women and 20% for men. Additionally, these fractures contribute to higher morbidity and mortality [3]. The diagnosis of osteoporosis is therefore significant for risk assessments of future fractures and sufficient treatment. According to the Bone Evaluation Study, 6.3 million patients aged 50 and above are affected in Germany. The prevalence of osteoporosis is increasing in correlation with demographic aging [4]. Although osteoporosis is considered a widespread disease, it is still frequently inadequately diagnosed and undertreated [4, 5]. This study aimed to reveal potential sources of error in the diagnostics of osteoporosis and evaluate pharmacological treatments in a real-world context.

2.1 Bone Mineral Density

Bone mineral density (BMD) is considered a key predictor of future fracture risk. A lowered BMD is associated with a significantly increased risk of fracture [6]. Various non-invasive instrumental examinations are available for assessing BMD.

2.1.1 Dual-Energy X-Ray Absorptiometry

Measuring BMD at the posterior-anterior lumbar spine and the hip is recommended as a fundamental diagnostic procedure for elevated risk of osteoporosis and fractures. Examination of areal bone mineral density (aBMD) using dual-energy X-ray absorptiometry (DXA) is considered the leading standardized method. The measurement uses X-ray beams at two energy levels to distinguish between bone and soft tissue based on their absorption rates. This enables the quantification of bone mineral content (BMC). Two-dimensional aBMD (g/cm^2) is calculated as the ratio of bone mineral content to the area of the assessed bone [7]. In the measuring process, a T-score is generated by assessing deviations from the average bone density of a young, healthy reference population. The classification of osteoporosis is based on a T-score of less than -2.5, osteopenia on a T-score between -2.4 and -1, and healthy bone density on a T-score greater than -1 [8]. Initially, this categorization was limited to postmenopausal women and was later extended by the International Society of Clinical Densitometry (ISCD) to include men over the age of 50 [9].

2.1.2 Quantitative Computed Tomography

Quantitative computed tomography (QCT) offers a practical and alternative technique for measuring bone mineral density [10]. QCT assesses an absolute volumetric measurement in mg hydroxyapatite /cm^3 independent of body size. Osteoporosis is defined at a volumetric bone mineral density (vBMD) below 80 mg/cm^3, osteopenia is characterized between 80 and 120 mg/cm^3. Axial QCT is also usually performed at the lumbar spine and the

proximal femur. QCT provides an ability to measure and analyze trabecular and cortical structures separately in regions of interest (ROI) [11]. Trabecular bone accounts for 20% of the total bone volume, with its proportion in the spine ranging from 66% in the lumbar region to 75% in the thoracic site. Trabecular bone shows a large surface area and a significantly increased metabolism compared to cortical bone [12]. QCT is not recommended by the DVO[2] guidelines as a routine diagnostic tool, mainly due to the insufficient prospective studies and lack of standardized reference data [13]. However, measurements with a significant reduction in vBMD should be included in the fracture risk evaluation and trabecular vBMD by QCT of the spine can be used to assess age-, condition-, and therapy-related changes [13, 14].

2.1.3 Comparison of Measurements from Dual-Energy X-Ray Absorptiometry and Quantitative Computed Tomography

Since DXA and QCT have relevant differences, an awareness of these features is significant for evaluating BMD results. DXA has a low radiation exposure with an effective dose of less than 1 to 18 µSv for both spine and femur scans and is considered an affordable and accessible method. In contrast, QCT measurements are associated with higher radiation exposure, typically with an effective dose between 50 and 100 µSv [15–17]. While DXA-derived aBMD provides two-dimensional integral values of combined cortical and trabecular bone algorithmically converted into T-scores, QCT offers an absolute three-dimensional vBMD measurement, allowing for separate assessments of trabecular and cortical bone [11]. The most reliable diagnostic thresholds have been established through femoral DXA assessment. When hip DXA measurements are compared with those obtained by alternative methods, including QCT, there are differences in both average values across the population and apparent bone loss rates. These discrepancies suggest that T-scores provide different levels of insight into fracture risk depending on the method and site of measurement. T-scores should therefore be limited to the use of DXA and should not be extrapolated from one measuring method to another [18].

As a result of the dimensionality differences, and variations in assessment of different bone compartments, the comparison of the measurement methods is challenging. For instance, the DXA provided relative T-scores based on population norms and the evaluation by QCT of absolute values is not directly comparable.

Although routinely used in clinical practice, DXA has its limitations. Spinal degeneration, vascular calcification, or focal lesions of the spine in elderly women and men [19, 20], can distort the measurement by reducing the intensity of X-rays. These confounding factors are particularly prevalent in geriatric populations [21, 22]. As a result, spinal osteoporosis is frequently underdiagnosed and under-evaluated due to overestimation of aBMD by DXA [23]. Postmenopausal women and older men with prevalent fragility and low-trauma fractures showed T-scores greater than -2.5 [24]. A study on a male population has demonstrated that fractures occurred in 27 to 45% of cases with only marginally decreased T-scores ranging from -1 to -2 [25]. Additionally, DXA T-scores were insufficient to diagnose severe osteoporosis in approximately half of the examined patients [26, 27]. The limitation in detecting fractures may be explained by the degenerative changes which are common in the elderly. Consequently, post-anterior DXA of the lumbar spine may have limited value, especially for older patients frequently affected by osteoporosis.

[2] The DVO (Dachverband Osteologie e.V.) is the interdisciplinary association of all scientific societies in Germany, Austria and Switzerland concerned with bone diseases.

These inaccuracies in BMD assessments by DXA can, however, be attributed not only to patient-related factors but also to operator-related issues including improper patient positioning, variations in the region of interest selected, and misinterpretations of results [28].

QCT is less susceptible to potential errors such as extra-vertebral sclerosis and degenerative changes in the spine [29]. The vBMD by QCT is considered a suitable predictor of existing fractures in postmenopausal women [30] and shows a significant association with the risk of incident vertebral fractures in older men [31]. Unlike DXA, QCT may not be affected by the possibility of BMD overestimation [32].

In previous studies comparing the measurement methods, QCT has proven to be superior to DXA in selective patient populations with high sensitivity for the detection of existing low-trauma fractures and for estimating the risk of future fractures [27, 30, 31], but still receives limited consideration in the clinical context.

The identification of fractures through different BMD measurements was examined in a study published as the initial scientific article of this cumulative thesis. The study comprised a main collective of 304 patients who received both DXA and QCT measurements within one year and involved two control groups, each including 50 reference patients. The inclusion criterion for the control was defined by the exclusive examination with DXA for group 1 or QCT for group 2 documented in the radiology internal system RIS. The findings indicated that DXA was inadequate for recognizing osteoporotic fractures in the main study cohort. In these analyses, vBMD by QCT correlated with the age of the patients. Among all patients, 87.7% of those with pathologic fractures had trabecular vBMD <80 mg/ml. Both trabecular and cortical measurements classified the presence of pathologic fractures with reduced vBMD. DXA and QCT proved to be effective measurements for the diagnosis of osteoporosis in the control groups [33].

2.2 Pharmacological Treatments of Osteoporosis

Osteoporosis is considered a chronic disease that often requires pharmacological intervention, particularly for individuals at high or extremely high risk of fracture. Deficits regarding adequate osteoporosis treatment are evident in both primary and secondary prevention of fractures in adults [5]. Pharmacological therapy aims to reduce fracture risk and increase BMD. Non-pharmacological osteoporosis interventions are recommended as adequate calcium and vitamin D supplementation, physical exercise, smoking cessation, and fall prevention [34]. Although non-pharmacological strategies have the potential to slow the progression of osteoporosis, they are not an appropriate treatment for patients at high fracture risk. The threshold for initiating pharmacological therapy follows a specific risk model for fracture estimation, as outlined in the DVO guidelines. Recommendations for pharmacological treatments are provided based on the T-Score by DXA, prevalent fractures, and calculated fracture risk depending on risk factors [13]. Other guidelines also recommend starting pharmacological therapy according to clinical factors like fragility fractures, reduced BMD determined using DXA, and the Fracture Risk Assessment Tool (FRAX) [34].

Pharmacological osteoporosis treatments can be categorized into antiresorptive and osteoanabolic strategies. Antiresorptive agents comprise five main classes of active substances, with bisphosphonates and denosumab recognized as the preferred first-line therapies [35]. Osteoanabolic drugs stimulate the formation of new bone and are primarily recommended in individuals with very high risk of fracture. In head-to-head studies, osteoanabolic teriparatide and romosozumab tended to lead to a greater BMD increase and a more effective fracture risk reduction than antiresorptive agents [36].

2.2.1 Antiresorptive Agents

Nitrogen-containing bisphosphonates have a high affinity for bone tissue. These substances act as farnesyl pyrophosphate synthase inhibitors, blocking the post-translational modification of various intracellular signaling proteins necessary for the function and survival of osteoclasts. This inhibition reduces osteoclast activity, leading to decreased bone resorption [37].

Alendronate and risedronate are commonly administered oral bisphosphonates, recognized for their clinical efficacy and safety profile. Both agents have been shown to significantly enhance aBMD as assessed by DXA, while mitigating the risk of vertebral and clinical fractures, respectively, in postmenopausal women and older men [38–40]. However, alendronate has shown greater improvements in aBMD and bone marker changes compared to risedronate [41].

Intravenous injection of bisphosphonates can avoid complicated administration and reduce common side effects of oral intake, such as gastrointestinal pathology, potentially enhancing patient adherence [42]. An annual infusion of 5 mg of zoledronic acid has been found to lower the risk of spinal and hip fractures, while also improving BMD and bone markers [43]. Intravenous administration of 1 mg ibandronate once-monthly significantly increases lumbar spine aBMD and has proven effective in patients showing low response to oral bisphosphonate treatment [44]. The accumulation of bisphosphonates in bone causes a depot effect, allowing a release for months to years after treatment cessation. Sustained effectiveness against fractures during the interruption of pharmacotherapy can be assumed for up to two years. A bisphosphonate holiday may be taken into consideration for patients with initially high fracture risk after 3 years of intravenous zoledronate or 5 years of stable treatment with oral bisphosphonates, provided their fracture risk is no longer deemed high. For individuals at very high fracture risk, bisphosphonate therapy should be continued for more than five years, and transitioning to an alternative treatment when interrupting bisphosphonate can be considered [34, 45].

Denosumab is a human monoclonal antibody injected subcutaneously as a 60 mg dose biannually. Denosumab imitates the effect of osteoprotegerin, an endogenous regulator of the receptor activator of nuclear factor kappa-B ligand (RANKL) mediated osteoclast activation. RANKL is expressed on the osteoblasts membrane and is considered an important factor for the differentiation, activation, and survival of osteoclasts. Through binding to RANKL with high affinity and specificity, denosumab blocks the interaction with the receptor activator of nuclear factor kappa-B (RANK) located on the membrane of osteoclasts and consequently inhibits the activity of osteoclasts and bone resorption [46]. In the FREEDOM study, denosumab significantly minimized the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women while also increasing areal BMD in the hip and lumbar spine [47]. In male patients with reduced BMD, a one-year treatment with denosumab was well-tolerated and induced significant gains in aBMD in all skeletal sites examined [48]. Discontinuation of denosumab carries the risk of a rebound effect, characterized by rapid loss of bone and elevated risk of multiple vertebral fractures. Denosumab therapy should therefore be continued; alternatively, a switch to potent bisphosphonates should be recommended [49]. Effects of interruptions of denosumab with subsequent rebound fractures could be observed during the Coronavirus Disease (COVID)-19 pandemic [50].

2.2.2 Osteoanabolic Agents

Teriparatide, a synthetically produced peptide, consists of the first 34 amino acids of parathyroid hormone (PTH), and is daily administered as a subcutaneous injection of 20 µg. Teriparatide stimulates the PTH-1 receptor, a G-

protein-coupled protein that provides mediations of numerous functions of PTH. PTH reduces apoptosis of osteoblasts and acts as a mitogen for cells of the osteoblast lineage. Therefore, teriparatide activates bone metabolism and improves skeletal microarchitecture [51]. The VERO study showed a substantial decrease in new vertebral and clinical fractures for teriparatide compared to risedronate [52]. In both postmenopausal women and men, treatment with teriparatide resulted in an improvement in aBMD assessed by DXA and can be considered a beneficial therapy [53, 54]. The duration of therapy with teriparatide should not exceed two years, and treatment is limited to a single course in a lifetime [51]. The monoclonal antibody romosozumab exerts its dual effect by binding to and inhibiting sclerostin, which enhances bone formation and reduces bone resorption. Subcutaneous injections over 12 months have been proven to reduce the risk of new vertebral and clinical fractures, as well as increase aBMD [55][3].

2.2.3 Sequences of Pharmacological Therapies

Since osteoporosis is classified as a chronic and progressive condition, various pharmacological agents need to be used in sequence for successful long-term treatment. Prior medications show a significant influence on the effect of subsequent therapy. Thus, the order of medications and long-term therapies assume major significance in treatment management.

Bisphosphonates and denosumab are recommended for long-term monotherapy. Alendronate and risedronate have been shown to continuously increase aBMD of the spine while causing a slight decrease in aBMD of the hip after 10 years of therapy [56]. Long-term studies on denosumab indicate its persistent impact on bone metabolism in the lumbar region and the hip after 8 years [57]. Denosumab should not be discontinued due to the rebound effect. Subsequent therapy with bisphosphonates after denosumab reduces the incidence of fractures. Additionally, patients who were pre-treated with bisphosphonates before starting denosumab have a significantly lower risk of rebound fractures compared to treatment-naïve patients [58].

Osteoanabolic medications are indicated for patients with high fracture risk. Teriparatide showed higher aBMD gains in treatment-naïve patients compared to those with medication history [53]. The duration of therapy with teriparatide and romosozumab is limited to 24 months and 12 months, respectively. Following treatment with osteoanabolic therapy, patients should switch to a potent therapy with anti-remodeling drugs to maintain the rebuilt bone substance [36]. Concerning contraindications to the administration of the specific drugs by multimorbid patients and previous medications in the medical history of many affected patients, optimal therapy sequences cannot be generalized and must be adapted to the individual circumstances of each patient in daily clinical practice.

2.2.4 Nonresponse to Pharmacological Treatment

The effectiveness of pharmacological treatments in increasing BMD has been frequently confirmed. However, few studies show a non-increase or decrease in BMD under pharmacological therapy. In 36% of patients receiving risedronate, and 20% of those treated with alendronate, BMD losses (<0% with DXA) at two or more sites were found after 12 months of treatment [41]. After one year of denosumab therapy following hip fractures, 20% of patients showed nonresponse to therapy defined as a persisting T-Score of <-3.0, reduction of >3% between baseline and scan after treatment, and occurrence of incident fractures during observation [59]. A transition from

[3] As romosozumab was only approved in December 2019 and was first authorized by the European Medicine Agency in April 2020, its effect on bone mineral density could not be evaluated in this study.

denosumab to teriparatide has been associated with gradual and temporary bone loss [60]. Non-increase in aBMD at the spine to teriparatide was detected in patients with prior denosumab treatment in real-world conditions [61]. Nonresponse to drug intervention for osteoporosis can arise more commonly in real-world scenarios than in controlled clinical studies, with an estimated occurrence rate of 10% or more. General causes of nonresponse include poor adherence to treatment, co-morbid conditions, vitamin D deficiency, and inherent lack of efficacy of the medications [62].

2.2.5 Monitoring of Pharmacological Therapy using Bone Mineral Density by Quantitative Computed Tomography

The widespread use of DXA is based on its international significance, the broad availability in the context of multi-center studies, the low radiation exposure, and the cost-effectiveness. Most interventional osteoporosis studies were performed using DXA [38, 43, 47, 53]. Osteoporosis is a health condition marked by age as an important risk factor. One in four women and one in 17 men aged 50 and above are affected. The frequency of osteoporosis-related fractures also increases with advancing age [4]. Accordingly, there is a corresponding rise in the use of pharmacological therapy among older patients. Present degenerative spinal pathology, which is prevalent in the elderly, can influence the outcomes of DXA [10, 22], while QCT can avoid these overestimations of BMD caused by degenerative changes [29, 32]. Additionally, trabecular vBMD of the spine QCT is useful for monitoring treatment-induced BMD changes [14].

In a subpopulation of the FREEDOM study, QCT-derived trabecular vBMD increased by 21.8% in the spine after 36 months of denosumab treatment [32]. Denosumab was found to provide greater gains in vBMD by QCT in treatment-naïve patients compared to those pre-treated with bisphosphonates [63]. Osteoanabolic therapies such as romosozumab and teriparatide also significantly increased both trabecular and cortical vBMD of the spine when measured with QCT [64].

Increases in vBMD assessed with QCT by pharmacological treatment sequences were additionally reported. Subsequent therapy to teriparatide showed trabecular spine vBMD increases of 8.8% for alendronate compared with no following treatment [65]. A follow-up therapy with 5 mg zoledronate after one year of overlapping teriparatide and denosumab treatment showed a 20.5% increase in trabecular vBMD after 15 months. However, this gain decreased to 3.1% after 42 months, suggesting that the vBMD increase of the spine was not sustained long-term when osteoanabolic therapy was followed by zoledronate [66].

Studies on treatment-related BMD changes with both measurement methods show higher improvements in BMD with DXA compared to QCT. For instance, it was revealed that the increase in bone mineral density with denosumab, based on DXA assessment, was significantly higher than the change measured by QCT. This was observed in both the treatment-naïve and the pre-treated group [63]. Additionally, comparisons of long-term courses indicate that QCT tended to show a greater decrease in BMD over time compared to DXA, where spine measurements showed only moderate reductions [66].

BMD monitoring of pharmacological therapies using QCT is increasingly applied in geriatric populations due to inconclusive DXA results, although research continues to focus on DXA as the gold standard.

Recent findings have demonstrated that pharmacological treatments are effective in preventing fractures in real-life scenarios [67], however, a study on the change in vBMD by QCT with various pharmacological agents in real life represents a novelty. In clinical practice, different effects of pharmacological treatments on vBMD by QCT were observed.

A comparison of the effects of diverse pharmacotherapies for osteoporosis on vBMD and fracture occurrence in a heterogeneous study population is investigated in the second scientific article of this doctoral project. Patients with at least two QCT scans and a decreased trabecular vBMD of <120 mg/ml were included in the study. The main focus was on estimating the yearly change in vBMD resulting from various pharmacological treatments, with the secondary objective being the incidence of fractures during the monitoring period. The study evaluated 1145 QCT scans from 402 individuals. Treatment-naïve patients showed an annual effect of - 2.35 mg/ml ($p<0.001$) on trabecular vBMD. The bisphosphonate groups were associated with a reduction in trabecular vBMD by -1.01 mg/ml ($p<0.001$) and -0.93 mg/ml ($p=0.015$) yearly, for oral and intravenous bisphosphonates, respectively. Therapy with denosumab showed decreasing but not statistically significant effects on trabecular vBMD. Teriparatide resulted in a 4.27 mg/ml annual improvement in trabecular vBMD ($p=0.018$). All pharmacological therapies demonstrated positive effects in comparison with non-treatment. However, fractures were reported with all medications during the observation period [68].

3 GERMAN ABSTRACT

Osteoporose gilt als häufige, jedoch oft unterdiagnostizierte und unzureichend therapierte Erkrankung des Skelettsystems, die sich in pathologischen Frakturen manifestiert. Zur Diagnostik, Einschätzung des Frakturrisikos und Beurteilung einer spezifischen medikamentösen Therapie wird die Knochenmineraldichte (BMD) herangezogen. Die Messung der BMD mit Dual-Röntgen-Absorptiometrie (DXA) gilt als Goldstandard. Aufgrund der Messmodalitäten kann es jedoch zu einer Überschätzung der Knochenmineraldichte kommen, die klinische Konsequenzen wie potenzielle Fehldiagnosen und defizitäre therapeutische Maßnahmen nach sich zieht. Die quantitative Computertomographie (QCT) stellt eine praktikable Alternative dar, die vor allem in geriatrischen Kollektiven Vorteile aufweist.

Die erste Studie im Rahmen dieser kumulativen Dissertation hatte die Zielsetzung, die Sensitivität von DXA und QCT hinsichtlich des Nachweises von osteoporotischen Frakturen zu vergleichen.

Patienten und Patientinnen ab dem 50. Lebensjahr, die innerhalb von 365 Tagen sowohl eine BMD-Messung mittels DXA der Lendenwirbelsäule und des Femurs als auch eine QCT der Wirbelsäule erhalten haben, wurden eingeschlossen. Die BMD ermittelt mit DXA sowie QCT und aufgetretene pathologische Frakturen wurden retrospektiv erfasst. Die BMD-Messungen wurden auf die Detektion vorliegender pathologischer Frakturen untersucht. Da eine potenzielle Verzerrung der Resultate durch das Einschlusskriterium von zwei BMD-Messmethoden in der Hauptpopulation nicht ausgeschlossen werden konnte, wurden additional Kontrollgruppen analysiert. Diese Referenzgruppen bestanden aus Patienten und Patientinnen, für die in Gruppe I ausschließlich DXA-Messungen und in Gruppe II ausschließlich QCT-Scans im radiologischen internen System dokumentiert waren. Für die statistischen Analysen wurden unter anderem Kreuztabellen zur Berechnung von Sensitivitäten und Receiver Operating Characteristic Curves herangezogen.

Insgesamt wurden 404 Patienten und Patientinnen analysiert. Davon erhielten 304 Probanden und Probandinnen DXA und QCT. Die Kontrollgruppen bestanden jeweils aus 50 Patienten und Patientinnen. Bei 33 von 114 (28,9 %) Patienten und Patientinnen mit pathologischen Frakturen wurde mittels DXA ein minimaler T-Score von <-2,5 festgestellt, entsprechend einer Osteoporose. Zudem zeigten 81 von 114 (71,1 %) Patienten und Patientinnen mit pathologischen Frakturen basierend auf DXA lediglich geringfügig verminderte oder gesunde BMD. QCT kategorisierte 100 von 114 (87,7 %) Patienten und Patientinnen mit pathologischer Fraktur mit osteoporotischer BMD von <80 mg/ml, kein Patient oder Patientin mit pathologischer Fraktur wies basierend auf QCT eine gesunde BMD auf. Sowohl die trabekuläre als auch kortikale BMD, ermittelt mit QCT, klassifizierte das Vorliegen von pathologischen Frakturen mit einer erniedrigten Knochenmineraldichte. Die DXA konnte das Vorliegen von Frakturen nicht vorhersagen. Aus Analysen der Kontrollgruppen resultierte, dass sich sowohl DXA als auch QCT in den Referenzgruppen für die Erkennung vorliegender pathologischer Frakturen eigneten.

Eine erfolgreiche medikamentöse Osteoporosetherapie senkt das Frakturrisiko und erhöht die Knochenmineraldichte (BMD). Antiresorptive und osteoanabole Pharmakotherapien werden durch Monitoring der BMD evaluiert. Die DXA gilt hier als Standardinstrument, das sowohl in der Forschung als auch auf Grund der praxisnahen Anwendung im klinischen Kontext überwiegend herangezogen wird. Die Aussagekraft der DXA ist aufgrund potenzieller Fehlerquellen, die besonders in der geriatrischen Bevölkerung auftreten, häufig eingeschränkt. Da pharmakologische Osteoporosetherapien in dieser Altersgruppe zunehmend indiziert sind, ist die Untersuchung alternativer BMD-Messmethoden zur Bewertung der medikamentösen Behandlung von großem Stellenwert.

Die zweite Studie dieses Promotionsprojektes evaluierte verschiedene medikamentöse Osteoporosetherapien mittels der durch QCT gemessenen BMD in einem Real-Life Kontext.

Hierzu wurden Patienten und Patientinnen ab dem 50. Lebensjahr mit erniedrigter trabekulärer BMD und mindestens zwei QCT-Untersuchungen eingeschlossen. Die aktuelle pharmakologische Osteoporosetherapie, die Therapiedauer, sowie die Vormedikation wurden retrospektiv erfasst. Ein Teil des Kollektivs wurde nach Studienbeginn prospektiv inkludiert. Sowohl die trabekuläre als auch die kortikale Knochenmineraldichte, ermittelt mit QCT der Wirbelsäule, wurden ausgewertet. Für jeden Patienten bzw. Patientin wurden identische Wirbelkörper in allen konsekutiven QCT-Untersuchungen evaluiert. Ein lineares gemischtes Regressionsmodel wurde zur Datenauswertung verwendet.

Im Rahmen der Studie wurden 1145 BMD-Messungen durch QCT von 402 Patienten und Patientinnen ausgewertet. Patienten und Patientinnen, die noch keine spezifische medikamentöse Osteoporosetherapie erhalten hatten, wiesen eine Reduktion der trabekulären Knochenmineraldichte von -2,35 mg/ml[4] pro Jahr auf. Ein Rückgang der trabekulären BMD von -1,01 mg/ml bzw. -0,93 mg/ml pro Jahr konnte zudem unter oralen Bisphosphonaten und intravenösen Bisphosphonaten geschätzt werden. Auswirkungen einer Denosumab Therapie auf die trabekuläre BMD zeigten abnehmende, aber nicht signifikante Effekte. Das osteoanabole Medikament Teriparatid war mit einem trabekulären Anstieg der BMD um 4,27 mg/ml pro Jahr assoziiert. Alle untersuchten Pharmakotherapien wirkten sich im Vergleich zu medikamentöser Nichtbehandlung positiv auf die trabekuläre BMD aus. Untersuchungen der Veränderungen der kortikalen Knochenmineraldichte gemessen mit QCT ergaben unter Denosumab eine Abnahme von -2,44 mg/ml pro Jahr. Weitere Analysen zu Effekten der medikamentösen Behandlung auf die kortikale BMD ergaben keine signifikanten Ergebnisse. In dem Beobachtungszeitraum der Studie waren alle Pharmakotherapien mit einem Auftreten pathologischer Frakturen assoziiert.

Die aufgeführten Studienergebnisse zeigen, dass sich die quantitative Computertomographie in bestimmten Populationen zur Diagnose einer Osteoporose und der Detektion prävalenter Frakturen eignet, während die Dual-Röntgen-Absorptiometrie in diesem Kontext begrenzte Anwendungsmöglichkeiten aufweist. Analysen des Monitorings pharmakologischer Osteoporosetherapien mittels QCT zeigten keinen Anstieg der trabekulären Knochenmineraldichte mit Bisphosphonaten und Denosumab. Im Gegensatz dazu war Teriparatid mit einer Zunahme der trabekulären BMD assoziiert. Somit resultieren antiresorptive Therapien und osteoanabole Therapie in dieser Studie in divergenten Effekten auf die mit QCT gemessene trabekuläre BMD. Die kortikale Knochenmineraldichte ermittelt mit QCT könnte sich zukünftig sowohl in der Osteoporosediagnostik als auch in der Therapieevaluation als hilfreich erweisen.

[4] Alle angegebenen Ergebnisse der geschätzten Veränderungen der Knochenmineraldichte (in mg/ml) wiesen eine statistische Signifikanz mit $p<0,05$ auf.

4 ABSTRACT

Osteoporosis is a prevalent skeletal disease manifesting in the occurrence of pathologic fractures. Bone mineral density (BMD) is assessed for diagnosing osteoporosis and evaluating the outcomes of pharmacological treatments. BMD measurement with dual-energy X-ray absorptiometry (DXA) is presently considered the gold standard in research and clinical practice. However, DXA may overestimate BMD as a result of measurement modalities. Regarding this limitation of DXA, quantitative computed tomography (QCT) presents a practicable alternative for measuring BMD, potentially offering greater accuracy and reduced susceptibility to measurement errors.

To evaluate the significance of DXA and QCT in the diagnostics of osteoporosis, the measurement methods were assessed for detecting prevalent pathologic fractures in the first study conducted. The study included patients who underwent both DXA and QCT examinations. BMD and the presence of fractures were recorded retrospectively. Since a potential bias of the results by the inclusion criterion of two BMD measurements in the main population could not be excluded, additional control groups were analyzed. Control group I comprised patients who had only undergone DXA examinations, while control group II included those who were only examined with QCT.

The study comprised 404 patients. Among these, 304 patients received DXA and QCT, while each control group consisted of 50 patients. DXA identified 33 out of 114 patients (28.9%) with pathologic fractures having a T-score <-2.5, which is categorized as osteoporosis. In comparison, QCT detected 100 out of 114 patients (87.7%) with fractures having a BMD <80 mg/ml, which is also classified as osteoporosis. QCT was effective in identifying osteoporotic fractures based on reduced trabecular and cortical BMD. However, DXA was inefficient in recognizing fractures. In the controls, both DXA and QCT were effective in detecting pathologic fractures.

The aim of pharmacological therapy is to prevent fractures and enhance BMD. BMD is used to assess the effects of such therapies, with DXA being the standard tool in both research and clinical application. Since DXA is particularly limited in the geriatric population, who are generally treated with pharmacological therapy, QCT has clinical significance. In patients with inconclusive or inaccurate DXA results, QCT can be recommended for reliable assessments.

The objective of the second article was to compare the effects of various pharmacological therapies on trabecular and cortical BMD determined by QCT. Patients with reduced BMD who had undergone at least 2 QCT scans were included. Data was collected on current and previous pharmacological treatments, as well as the occurrence of osteoporotic fractures. Trabecular and cortical BMD measured by QCT were assessed.

In the study, a total of 1145 QCT scans from 402 patients were examined. Bisphosphonate therapies were estimated to decrease trabecular BMD by -0.93 to -1.01 mg/ml per year ($p<0.05$), depending specifically on whether the administration was intravenous or oral. Decreasing but not significant changes in trabecular BMD were observed in patients treated using denosumab. The effect of teriparatide administration on trabecular BMD was estimated to result in an annual increase of 4.27 mg/ml ($p = 0.018$). All pharmacological treatments demonstrated advantageous impacts on trabecular BMD when compared to no medication history. The occurrence of fractures was observed in all pharmacological therapies during the monitoring period.

The results of the studies suggest that QCT is efficient for both the diagnostics of osteoporosis and the detection of pathologic fractures in a specific patient population, whereas DXA is limited in this context. Analysis of pharmacological therapies on BMD measured by QCT revealed contrasting effects for antiresorptive agents (bisphosphonates, denosumab) and osteoanabolic medication (teriparatide) on trabecular BMD. Additionally, cortical BMD of the spine derived by QCT could prove useful in diagnostics and therapy evaluation.

5 FIRST PUBLICATION

Boehm E, Kraft E, Biebl JT, Wegener B, Stahl R, Feist-Pagenstert I. Quantitative computed tomography has higher sensitivity detecting critical bone mineral density compared to dual-energy X-ray absorptiometry in postmenopausal women and elderly men with osteoporotic fractures: a real-life study. Archives of Orthopaedic and Trauma Surgery. 2024;144(1):179-88. doi: 10.1007/s00402-023-05070-y.

6 SECOND PUBLICATION

Boehm E, Sauer C, Baur-Melnyk A, Biebl JT, Harada S, Wegener B, Kraft E, Stahl R, Feist-Pagenstert I. Real-life effects of pharmacological osteoporosis treatments on bone mineral density by quantitative computed tomography. Journal of Bone and Mineral Metabolism. 2024;42(6):741-53. doi: 10.1007/s00774-024-01553-z.

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