UNIVERSIDADE DE BRASÍLIA

Faculdade de Ciências da Saúde

Programa de Pós-Graduação em Odontologia

Tese de Doutorado

Análise tomográfica mandibular e vertebral para avaliação de osteoporose e de risco de fratura em mulheres na pós-menopausa.

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Brasília, 31 de março de 2022

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Tese de Doutorado apresentada ao programa de Pós-Graduação em Odontologia da Universidade de Brasília, como requisito para obtenção do título de Doutora em Odontologia.

Orientador: Prof. Dr. André Ferreira Leite

BRASÍLIA

2022

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Data da defesa: 31/03/2022

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Dedico este trabalho às mulheres cientistas que são tão pouco reconhecidas, mas mudaram o mundo e a história da ciência em diversas áreas.

Minha pequenez diante destas aumenta incrivelmente minha enorme admiração.

Agradecimentos

Ao SUS, conquista brasileira, pois sem esse sistema nada teria acontecido.

À minha mãe pelo amor e pelo incentivo em percorrer o caminho acadêmico.

Ao meu pai pelo amor e por sempre proporcionar o melhor para minha vida.

Ao meu orientador André, que é uma pessoa incrível e que de forma sempre positiva me guiou, me compreendeu e me ensinou muito nos últimos anos.

À equipe de Diagnóstico da Unidade de Saúde Bucal do Hospital Universitário de Brasília pelo suporte e assistência.

Ao meu colega Bruno por toda a parceria durante a realização das pesquisas.

LISTA DE ABREVIATURAS E SIGLAS

DMO	Densidade mineral óssea
ANOVA	Análise de Variâncias
AUC	*Area under the Curve* (área abaixo da curva ROC)
BMD	*Bone Mineral Density*
CF	Colo Femoral
FT	Fêmur Total
DXA	*Dual-energy X-ray absorptiometry*
QUS	*Quantitative ultrasound*
ECM	Espessura da cortical mandibular
ECMp	Espessura da cortical mandibular em reconstrução panorâmica
ECMt	Espessura da cortical mandibular em corte transversal/transaxial
g/cm^2	Gramas por centímetro quadrado
SUS	Sistema Único de Saúde
mm	Milímetro
MOI	Mandibular Osteoporosis Index
r	Coeficiente de Correlação
IMCT	Índice Mandibular Cortical Tomográfico
L1	Primeira vértebra lombar
L4	Quarta vértebra lombar
HUB	Hospital Universitário de Brasília
kVp	Pico de quilovoltagem
TCFC	Tomografia computadorizada de feixe cônico
TCFL	Tomografia computadorizada de feixe em leque
mA	Miliamperagem
χ^2	Qui-quadrado
ROC	*Receiver Operating Characteristic*
DP	Desvio-padrão

IC	Intervalo de confiança
≤	Menor ou igual
>	Maior
<	Menor
VPP	Valor preditivo positivo
VPN	Valor preditivo negativo

RESUMO

A osteoporose é uma doença esquelética relacionada à perda da resistência óssea que predispõe a fraturas por trauma mínimo. A resistência óssea é dada pela densidade mineral óssea (DMO) e pela qualidade óssea. As fraturas mais comuns relacionadas à doença, como as de vértebra e quadril, diminuem a qualidade de vida dos indivíduos afetados, aumentam o número de internações hospitalares e podem levar ao aumento da mortalidade, principalmente em idosos que, juntamente com as mulheres na pós-menopausa, representam o grupo de maior risco para a doença. Apesar da verificação da DMO pelo exame de densitometria por dupla emissão de raios X (DXA) ser ainda considerada o padrão-ouro para o diagnóstico da osteoporose, muitas pessoas com DMO normal apresentam fragilidade óssea e, consequentemente, fraturas. Além disso, as fraturas por osteoporose são geralmente assintomáticas e, por isso, a doença é considerada como silenciosa. São necessários, portanto, métodos de rastreamento de pessoas com baixa DMO e com risco aumentado de fraturas, o que poderia diminuir o impacto sócio-econômico da doença. Visto que a tomografia computadorizada de feixe cônico (TCFC) é um exame muito utilizado na população idosa, principalmente para planejamento de implantes e, que alterações mandibulares já foram relatadas em pacientes com osteoporose, torna-se necessário verificar este exame como instrumento auxiliar no diagnóstico da doença. Nesse sentido, o presente estudo teve como objetivo geral verificar alterações ósseas mandibulares em exames de TCFC de mulheres na pós-menopausa. Como objetivos específicos, este estudo verificou se medidas qualitativas e quantitativas na cortical mandibular poderiam predizer o diagnóstico da doença. Além disso, alterações trabeculares também foram verificadas por meio do cálculo da dimensão fractal (DF) em dois sítios ósseos da TCFC: na mandíbula e na região da segunda vértebra cervical (que aparece no escaneamento da mandíbula). Como último objetivo específico, o estudo analisou se a espessura da cortical mandibular apresentava relação com o risco de fratura medido pela ferramenta FRAX. O estudo utilizou, como critério de inclusão, mulheres na pós-menopausa com exames prévios de densitometria óssea e TCFC com boa qualidade. Os critérios de exclusão foram uso de medicações que afetassem o metabolismo ósseo e a presença de outras doenças osteometabólicas com exceção da osteoporose. A amostra final consistiu de 103 pacientes, sendo 52 com DMO normal e 51 com diagnóstico densitométrico de osteoporose. Houve a comparação dos parâmetros ósseos mandibulares corticais e trabeculares e a avaliação das medidas de acurácia para predizer osteoporose nos dois grupos avaliados, resultando em três artigos, dois já publicados. A mensuração da DF dos artigos B e C foi realizada no programa ImageJ. O primeiro artigo avaliou qualitativamente e quantitativamente a cortical mandibular, com o estabelecimento de um novo índice denominado índice mandibular tridimensional para osteoporose (3D MOI). Este índice, juntamente com a idade, apresentou uma boa acurácia para predizer o diagnóstico densitométrico de osteoporose, com área abaixo da curva de 0,8. No segundo artigo, a análise da DF não demonstrou boa acurácia e reprodutibilidade para predizer o diagnóstico densitométrico, apesar dos valores de DF terem sido significativamente menores em pacientes com osteoporose quando comparados aos de mulheres com DMO normal. Por fim, o último artigo demonstrou que a espessura da cortical mandibular foi capaz de predizer o risco de fratura de quadril quando utilizado o ponto de corte do FRAX brasileiro de 3%. Para esta finalidade, 46 mulheres que responderam à ferramenta FRAX foram relacionados aos dados da espessura da cortical mandibular. A espessura da cortical mandibular

apresentou área abaixo da curva ROC de 0,903 para predizer o maior risco de fratura do quadril (acima de 3¨%). Como conclusão final destes estudos, a análise da TCFC demonstrou acurácia para predizer o diagnóstico densitométrico de osteoporose, com base em um novo índice cortical (artigo A) e também o maior risco de fratura de quadril, com base na análise da espessura da cortical mandibular (artigo C). A análise da DF não demonstrou boa acurácia para esta finalidade na população estudada (artigo B).

Palavras-chave: osteoporose; fratura por osteoporose; tomografia computadorizada de feixe cônico; densidade óssea

ABSTRACT

Osteoporosis is a skeletal disease related to loss of bone strength that predisposes to fractures from minimal trauma. Bone strength is given by bone mineral density (BMD) and bone quality. The most common fractures related to the disease, such as vertebral and hip fractures, decrease the quality of life of affected individuals, increase the number of hospital admissions, and may lead to increased mortality. Elderly people and postmenopausal women represent the main risk groups for the disease. Although BMD measurement by dual-energy X-ray absorptiometry (DXA) is still considered the gold standard for the diagnosis of osteoporosis, many people with normal BMD present bone fragility and, consequently, fractures. Furthermore, osteoporosis fractures are usually asymptomatic and therefore the disease is considered to be silent. Therefore, methods to screen people with low BMD and at increased risk of fractures are crucial, aiming at decreasing the social and economic burden of the disease. Cone-Beam Computed Tomography (CBCT) exam is widely used in the elderly population, especially for implant planning, and mandibular changes have already been reported in patients with osteoporosis. Accordingly, it is necessary to verify whether this exam could serve as an auxiliary tool for identifying the disease and the highest fracture risk group. By this way, the main aim of this study was to verify mandibular bone changes in CBCT scans of postmenopausal women. As specific aims, this study investigated whether qualitative and quantitative measurements in the mandibular cortex could predict the diagnosis of the disease. Moreover, trabecular changes were also verified by calculating the fractal dimension (FD) in two bone sites of CBCT: in the mandible and in the region of the second cervical vertebra (which appears in the mandible scan). As a last specific objective, the study analyzed whether the mandibular cortical thickness was related to fracture risk evaluated by the FRAX tool. The inclusion criteria were postmenopausal women with previous bone densitometry and CBCT scans with good quality. Exclusion criteria were the use of medications affecting bone metabolism and the presence of other osteometabolic diseases except osteoporosis. The final sample consisted of 103 patients, 52 with normal BMD and 51 with densitometric diagnosis of osteoporosis. The comparison of cortical and trabecular mandibular bone parameters and the evaluation of the accuracy measures for predicting osteoporosis in both groups resulted in three articles, two of which have already been published (articles A and B). FD calculations were performed using ImageJ software. The first

article evaluated the mandibular cortical bone qualitatively and quantitatively, establishing a new index called the three-dimensional mandibular osteporotic index (3D MOI). This index, together with age, showed a good accuracy to predict the densitometric diagnosis of osteoporosis, with an area under the ROC curve of 0.8. In the second article, FD did not show good accuracy and reproducibility for predicting the densitometric diagnosis, although FD values were significantly lower in patients with osteoporosis when compared with those of women with normal BMD. Finally, the last article demonstrated that the mandibular cortical thickness was able to predict the hip fracture risk when using the Brazilian FRAX cut-off point of 3%. For this purpose, 46 women who responded to the FRAX tool were related to the mandibular cortical thickness data. The mandibular cortical thickness showed an area under the ROC curve (AUC) of 0.903 to predict the highest risk of hip fracture (above 3¨%). As a final conclusion of these studies, CBCT analysis showed accuracy to predict the densitometric diagnosis of osteoporosis, based on a new cortical index (article A) and also the highest risk of hip fracture, based on the analysis of mandibular cortical thickness (article C). On the other hand, FD analysis did not demonstrate good accuracy for this purpose in the studied population (article B).

Keywords: osteoporosis; osteoporotic fractures; cone-beam computed tomography; bone density

SUMÁRIO

INTRODUÇÃO

A osteoporose é uma doença esquelética muito comum e caracterizada por diminuição na resistência óssea. A resistência óssea reflete a integração entre a densidade mineral óssea (DMO) e a qualidade óssea (NIH, 2001). Na presença da osteoporose, a fragilidade óssea é aumentada e, consequentemente, é aumentada também a predisposição dos indivíduos doentes à fratura por trauma mínimo. Estas fraturas se caracterizam por caracterizadas por fraturas em quedas da própria altura ou fraturas por baixo impacto que não ocorreriam em situação de normalidade óssea (Borgström et al., 2020).

A osteoporose é considerada um dos maiores problemas de saúde pública devido ao seu impacto socioeconômico em decorrência das fraturas, e a conscientização pública sobre a osteoporose e suas consequentes fraturas por fragilidade é baixa em muitos países (Blain et al., 2016, Marinho et al., 2014, Atik et al., 2006). Por ser caracterizada como uma doença silenciosa, a osteoporose não apresenta manifestações clínicas até que haja a presença da primeira fratura. A população mais atingida são indivíduos idosos e mulheres na pós-menopausa. Diante do envelhecimento da população, ferramentas alternativas de rastreio da doença e de pessoas com risco aumentado de fratura são necessárias para realização de diagnóstico precoce e do tratamento. (Bomfim & Camargos, 2021; Radominski et al., 2017).

O diagnóstico da osteoporose é feito principalmente pela análise da densidade mineral óssea (DMO), por meio da densitometria por dupla emissão de raios X (DXA). A baixa DMO somada a outros fatores de risco é taxativa para indicação ao tratamento da osteoporose e redução do risco à fratura (IOF, 2022; Kocijan et al., 2020; Barron et al., 2020; Radominski et al., 2017). Apesar do DXA ser considerado o padrão ouro

para o diagnóstico da doença, o seu alto custo e a menor disponibilidade impedem a sua utilização para rastreamento da osteoporose e alternativas como exames por tomografia computadorizada e ressonância magnética tem sido estudadas para esse propósito (Tse et al., 2021, Kocijan et al., 2020;).

Os índices radiomorfométricos em exames de imagem odontológicos, como radiografia panorâmica da face e tomografia computadorizada de feixe cônico (TCFC) há alguns anos vêm sendo estudados como uma das ferramentas alternativas acessíveis para diagnóstico precoce da osteoporose e de outras doenças que também apresentam manifestação óssea, como doença renal crônica (Mohamed et al., 2021), hiperparatireoidismo (Queiroz et al., 2019), osteogênese imperfeita (Apolinário et al., 2016), anemia falciforme (Neves et al., 2012), doença celíaca (Neves et al., 2020) e diabetes (Kurşun-Çakmak & Bayrak, 2018).

Tendo em vista o impacto mencionado da osteoporose na população, especialmente relacionado às fraturas por trauma mínimo, bem como a crescente utilização dos exames de TCFC em odontologia, faz-se necessário verificar se análises do osso mandibular podem auxiliar na identificação de indivíduos com a doença e com risco aumentado de fratura, a consequência principal da doença. Esses foram os objetivos principais desse trabalho. Desta forma, esta tese está dividida por capítulos. No primeiro capítulo, será ainda apresentada uma breve revisão narrativa da literatura. O segundo capítulo descreve os objetivos do estudo e a metodologia empregada. O terceiro capítulo apresenta dois artigos publicados durante o curso de doutorado, no qual o artigo A apresenta um novo índice mandibular baseado em análises qualitativas e quantitativas em TCFC que, juntamente com a idade, apresentou acurácia para identificar mulheres na pós-menopausa com osteoporose e o artigo B demonstrando as limitações e dificuldades da análise da dimensão fractal

do trabeculado em TCFC para identificação destes pacientes. O quarto capítulo trata-se de um artigo em elaboração, que avaliou medidas corticais e trabeculares em TCFC para identificação de indivíduos com risco aumentado de fraturas analisados pela ferramenta *Fracture Risk Assessment Tool* (FRAX). A análise da cortical mandibular foi capaz de identificar mulheres com risco maior de fratura do quadril. O quinto e último capítulo discute os principais resultados desses artigos e as perspectivas para identificação de doenças osteometabólicas em imagens odontológicas.

1. CAPÍTULO 1 – REVISÃO DE LITERATURA

1.1 REVISÃO DE LITERATURA

1.1.1 Fatores de risco e impacto da fratura por osteoporose

A pirâmide etária brasileira vem se modificando de acordo com o crescimento da população idosa. Segundo o IBGE (2021), dos 210 milhões brasileiros, 37,7 milhões são pessoas idosas, ou seja, pessoas que têm 60 anos ou mais. Também segundo o IBGE, pode-se ver a projeção da evolução de grupos etários até o ano de 2060, com o envelhecimento progressivo da população brasileira, seguindo uma tendência mundial.

Devido ao aumento da expectativa de vida da população, o Brasil se encontra em transição epidemiológica. O perfil epidemiológico brasileiro passa a acompanhar esse processo de envelhecimento e se depara com um aumento de enfermidades crônicas e múltiplas. Com o crescimento da população idosa, há um aumento epidemiológico de doenças crônicas já conhecidas como diabetes, hipertensão, problemas vasculares, artrite e osteoporose (Baccaro et al., 2015). Nos anos de 2020 a 2022 a pandemia causada pelo coronavírus COVID-19 afetou gravemente os idosos e de maneira direta e indireta impactou no diagnóstico e no tratamento de doenças crônicas, incluindo a osteoporose, diminuindo também o rastreamento da doença (Yu & Tsourdi 2020.; Cromer e Yu, 2021). O rastreamento da doença é entendido como uma importante necessidade, visto que o ortopedista e o traumatologista não podem se deter apenas ao tratamento cirúrgico da fratura osteoporótica, uma vez que a fratura compromete a qualidade de vida do indivíduo acometido e também promove grandes gastos ao Sistema Único de Saúde (SUS) (Oliveira et al., 2021).

Alguns autores estimam que cerca de 200 milhões de pessoas no mundo tenham osteoporose, e a prevalência da osteoporose em mulheres na pós-

menopausa no Brasil varia entre 15 e 33% (Radominski et al., 2017; Reginster e Burlet, 2006).

No Brasil, cerca de 10 milhões de pessoas são diagnosticadas com osteoporose e é estimado que o número de fraturas de quadril por ano deve chegar a 160 mil até 2050. Estimava-se que o número de fraturas de quadril em 2015 era de 80.640, das quais 23.422 eram em homens e 57.218 em mulheres. Em 2040, espera-se que o número de fraturas de quadril aumente para 55.844 na população masculina e para 141.925 na população feminina, um aumento de 238 e 248%, respectivamente. Apenas em 2010, o SUS teve um gasto de aproximadamente R$81milhões para o atendimento ao paciente com osteoporose e vítima de quedas e fraturas (Stolnicki & Oliveira 2016).

A osteoporose é, portanto, uma doença esquelética frequente, que se caracteriza pela diminuição da resistência óssea, que consiste na integração entre a DMO e a qualidade óssea. Com a diminuição da resistência óssea, causada pela doença, aumenta a fragilidade óssea e, consequentemente, o risco de fraturas por trauma mínimo (NIH, 2001). A fratura por fragilidade óssea é a maior expressão clínica da doença. Fratura por fragilidade é definida como uma fratura causada por um trauma que seria insuficiente para fraturar um osso saudável, resultado de uma redução da resistência óssea a compressão ou a torção (WHO, 1998). Um indivíduo com fratura por baixo trauma do punho, quadril, úmero proximal ou tornozelo tem quase quatro vezes mais risco para fraturas futuras. Cerca de 50% de todos os casos de fratura de quadril vêm de 16% da população feminina pós-menopausa com histórico de fratura (Stolnicki & Oliveira 2016).

A osteoporose pós-menopausa é a que ocorre devido à queda do hormônio estrogênio. Na menopausa, ocorre o aumento da renovação óssea e diminuição da

formação óssea em cada unidade de remodelação, o que conduz a uma perda de massa óssea. O risco de osteoporose depende tanto da massa óssea máxima alcançada nos anos da idade adulta jovem quanto do índice de perda da massa nas épocas posteriores. O pico de massa óssea geralmente não é alcançado antes dos 30 anos e o estilo de vida é um fator determinante para o desenvolvimento da osteoporose. A diminuição do estrogênio é a grande responsável pela gênese da osteoporose após a menopausa, sendo a perda óssea mais intensa nos cinco anos que se seguem a ela. Por isso, essa condição é mais frequente e mais dramática nas mulheres, sendo que as mulheres, após essa fase de vida, chegam a perder cerca de 40 a 50% da massa óssea até o final da vida. Essa perda óssea leva ao afilamento do osso cortical e ao desgaste da estrutura do trabeculado ósseo (NAMS 2021; Kanis et al., 2019, Rossi et al., 2018, Radominski et al., 2017).

O estudo da osteoporose tem como finalidade não só proporcionar melhor tratamento e qualidade de vida, mas também proporcionar um melhor rastreamento e diagnóstico precoce da doença. Afinal, trata-se de uma doença silenciosa, cujo diagnóstico geralmente é feito após a ocorrência da fratura, consequência mais grave da doença. As fraturas de antebraço, fêmur e as de vértebras são as que ocorrem com maior frequência (NAMS 2021, Barron et al., 2020), sendo que as fraturas de vértebra e, principalmente, as de fêmur são as que geram mais custos relacionados às internações e tratamento (Moriwaki & Noto, 2016). A identificação de mulheres na pós-menopausa com fatores de risco para fratura facilita a intervenção precoce, auxiliando na manutenção ou no aumento de massa óssea e consequente redução no risco de fratura (Barron et al., 2020; Coughlan & Dockery 2014).

A avaliação da DMO é crucial para o diagnóstico e manejo da osteoporose visto que há estreita relação com a fragilidade óssea e o risco à fratura.

1.1.2 Exames por imagem para avaliação da densidade mineral óssea e da qualidade óssea

A mensuração da qualidade óssea não pode ser realizada apenas por meio de exames clínicos. Para isso, são utilizados exames de imagem que podem detectar alterações na microarquitetura óssea, avaliando a diminuição da espessura das corticais ósseas e o aumento da radiolucidez do tecido ósseo e alterações no trabeculado ósseo (Fan et al., 2016; Manhard et al. 2016).

A massa óssea, a densidade óssea e a morfologia óssea podem ser avaliadas por exames radiográficos e pela densitometria óssea. A massa óssea pode ser avaliada por diversos exames, entre eles o exame de densitometria de duplo feixe de raios X (DXA - Dual Photon Absorptiometry), a tomografia computadorizada quantitativa e a ultrassonografia quantitativa (QUS - quantitative ultrasound) (Manhard et al, 2016; Fan et al, 2016).

O exame padrão para a mensuração da DMO é a DXA (Kanis et al., 2019) e suas principais vantagens estão na sua fácil manipulação e reprodutibilidade, além de oferecer uma baixa dose de radiação aos pacientes (Fan et al. 2016). A DMO pode ser mensurada em sítios centrais, tais como coluna lombar e colo de fêmur (Figura 1), ou em sítios periféricos, como punho.

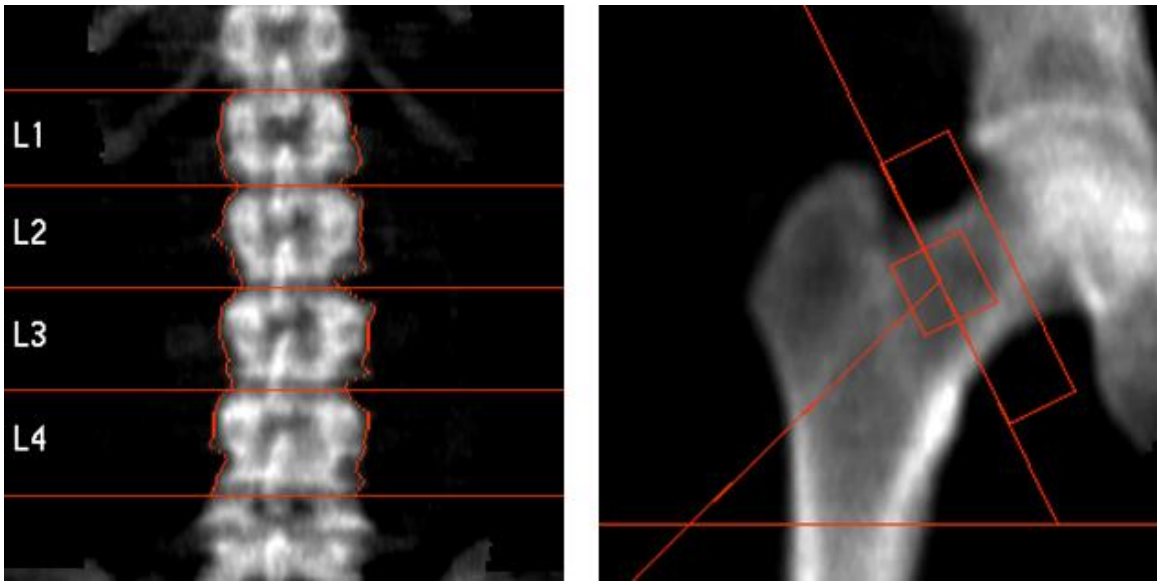

Fig1A **Fig1B**

Figura 1 - Imagem de exame por DXA da coluna lombar (Fig1A) e do quadril (Fig 1B). Fonte: Banco de imagens das pacientes avaliadas na pesquisa.

A capacidade do exame de DXA de avaliar diferentes sítios também o torna a modalidade de diagnóstico mais utilizada para detecção e acompanhamento da osteoporose. (Høiberg et al. 2016).

Segundo a classificação da Organização Mundial da Saúde (WHO, 2004) os resultados da DMO medida por DXA são padronizados como valores T-score, e esses valores são baseados no desvio padrão (DP) da DMO medida nos pacientes e comparada com a média de DMO de um adulto jovem. Os critérios diagnósticos baseiam-se conforme explicitado abaixo:

- T-score ≤ -1,0 desvio-padrão ⇒ paciente normal
- –2,5 < T-Score < -1,0 ⇒ osteopenia;
- T-Score ≤ –2,5 desvios-padrão ⇒ osteoporose;

São indicadores da necessidade da realização do exame de densitometria óssea:

- pós-menopausa com histórico familiar de fraturas;

- processo de menopausa com risco clínico de fraturas;
- homens e mulheres com histórico de risco a fratura;
- adultos com doenças associadas à redução da densidade mineral óssea;
- adultos que utilizam medicamentos associados à redução da densidade mineral óssea;
- adultos que utilizam medicação para tratamento da osteoporose;
- homens com menos de 70 anos que apresentam risco a fratura. (Messina et al., 2016).

A avaliação do risco de fratura também pode representar uma maneira de análise da necessidade de mensuração da DMO. Um dos principais métodos utilizados atualmente para análise do risco de fratura é o algoritmo FRAX (*Fracture Risk Assessment Tool*) que é descrito com mais detalhes no tópico “Risco de fratura e FRAX”. Em pacientes com alto risco para fraturas em resultado dado pela DMO ou pelo FRAX, é sugerido que a avaliação da DMO seja repetida a cada um ou dois anos, à critério médico (Radominski et al., 2017).

Segundo a IOF (2022), o profissional de saúde ao realizar a anamnese do paciente deve levar em conta históricos de fratura e precisa utilizar a ferramenta FRAX para avaliar o risco de fratura óssea. A depender do resultado dado pelo FRAX, todos os pacientes homens e mulheres com mais de 65 anos de idade devem realizar a densitometria óssea por DXA (https://www.osteoporosis.foundation/patients/diagnosis).

1.1.3 Risco de fratura e FRAX

A osteoporose afeta todos os ossos do corpo, entretanto as fraturas ocorrem com mais frequência nas vértebras, no pulso e no quadril. As fraturas osteoporóticas na bacia, no antebraço e na parte inferior da perna também são comuns. A osteoporose em si não é dolorosa, mas os ossos fraturados podem causar dores severas, deficiências graves e até a morte (IOF, 2022; Bomfim & Camargos 2021).

Tanto as fraturas de quadril como as de coluna estão associadas a um maior risco de mortalidade, 20% das pessoas que sofrem uma fratura de quadril morrem no prazo de 6 meses após a ocorrência da fratura (WHO, 2004, Blain et al. 2012).

O objetivo principal do tratamento da osteoporose é reduzir o risco à fratura pela fragilidade óssea e para isso é necessário reconhecer quem são os indivíduos que necessitam de intervenção (Albergaria & Paula 2019). Pacientes com fraturas osteoporóticas recentes são de alto risco para novas fraturas e, muito frequentemente, não recebem orientação e tratamento após a primeira fratura. Os fatores de riscos mais associados a fratura são gênero feminino, menopausa, histórico familiar de fratura, baixa DMO do colo femoral, baixo peso, sedentarismo, tabagismo, etilismo, uso prolongado de prednisona e dieta pobre em cálcio (Barron et al. 2020; WHO, 2004).

Pinheiro et al. (2010) realizaram um estudo epidemiológico, denominado BRAZOS (The Brazilian Osteoporosis Study), com 2.420 indivíduos provenientes das cinco regiões brasileiras, a fim de identificar os principais fatores de risco associados à fratura por trauma mínimo. Como resultado para homens, encontraram o tabagismo, baixa qualidade de vida e diabetes melito como os principais fatores clínicos de risco. Para as mulheres, os resultados mais relevantes foram idade avançada, menopausa precoce, sedentarismo, baixa qualidade de vida, maior consumo de fósforo, diabetes

melito, quedas, uso crônico de benzodiazepínicos e história familiar de fratura de fêmur após os 50 anos em parentes de primeiro grau.

O algoritmo FRAX é uma ferramenta online gratuita, criada na universidade de Sheffield na Inglaterra e posteriormente lançada em 2008 pela Organização Mundial de Saúde (OMS), para auxílio na identificação de homens e mulheres com risco de fratura óssea. A ferramenta já foi validada em diversos países, incluindo o Brasil, para avaliar o risco de fraturas de quadril e de fraturas maiores por osteoporose em 10 anos. Para essa validação, foram realizados diversos estudos de coorte e a calibração usou banco de dados epidemiológicos de fratura de quadril e mortalidade (Kanis et al.,2018; Zerbini & Paula, 2018).

O FRAX se baseia na coleta de informações do paciente como idade, gênero, peso, altura, e DMO do colo femoral (opcional), se o paciente já sofreu alguma fratura, se os pais já tiveram fraturas de quadril, se fuma ou consome bebidas alcoólicas, faz uso de glicocorticoides há mais de três meses, tem artrite reumatoide ou se tem alguma doença relacionada à osteoporose secundária. O conjunto destes dados permite calcular o risco de fraturas relacionadas à osteoporose (fraturas de quadril e fraturas maiores) no período de 10 anos após o cálculo (Kanis et al., 2018).

O uso de FRAX, na prática clínica, exige uma consideração da probabilidade de fratura na qual intervir, tanto para o tratamento quanto para o teste de DMO. A ferramenta FRAX é calibrada de acordo com a região epidemiológica, levando em conta de taxas de mortalidade e de fraturas ósseas específicas de cada país e está disponível em 63 países e em 32 línguas (Albergaria & Paula, 2019). O FRAX Brasil está disponível na internet desde 2013 (Figura 2).

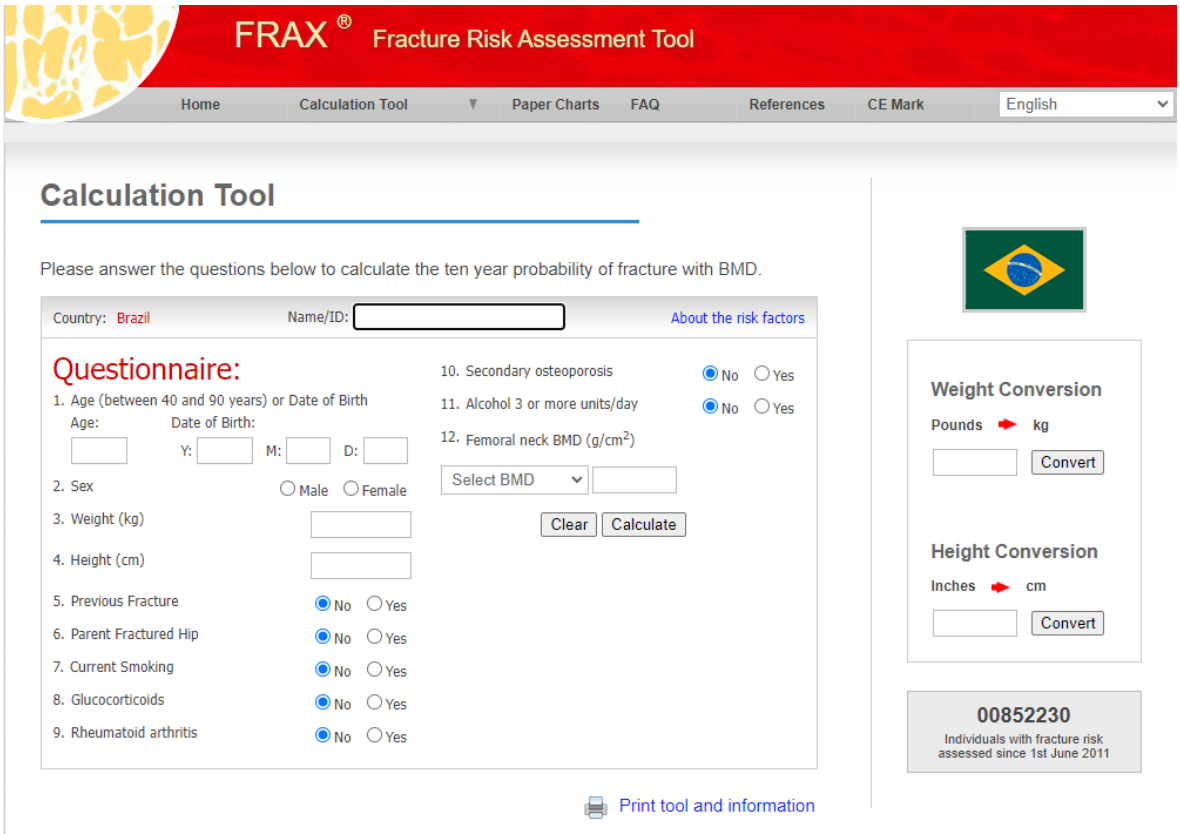

Figura 2 – Questionário da ferramenta FRAX.
Fonte: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=55

Pacientes que apresentam histórico de fratura por fragilidade e/ou pacientes com T-score igual ou menor que 2,5 na avaliação da coluna lombar e do fêmur devem ser direcionados para o tratamento medicamentoso. Já os pacientes sem histórico de fratura, o tratamento deve ser indicado de acordo com o cálculo do FRAX Brasil e as diretrizes da *National Osteoporosis Guideline Group* da Universidade de Sheffield, Inglaterra (Radominski et al. 2017).

Existem estudos brasileiros, porém o valor real do risco de fratura para brasileiros não foi estabelecido, sendo utilizado o valor padrão de 3% como ponto de corte para fratura no quadril e 15% para fraturas maiores por osteoporose (Albergaria & Paula, 2019, Zerbini & Albergaria, 2018).

Recentemente, foram sugeridos ajustes ao FRAX como por exemplo a inserção de fraturas vertebrais como risco de fratura osteoporótica. Essa ideia foi baseada em evidências que indicam que o risco de acontecer uma fratura secundária é imediatamente maior após a primeira fratura não-patológica, com risco alto de fratura nos 2 anos subsequentes. A ferramenta FRAX indica a probabilidade de fratura sem levar em conta a data do ocorrido e assim pode subestimar a probabilidade de fratura onde a fratura anterior ocorreu no período menor ou igual a 2 anos. El Miedany (2020) também aponta a relevância do escore do osso trabecular ou *trabecular bone score* (TBS) do exame de DXA da coluna para auxiliar no cálculo pelo FRAX para predizer risco de fratura (El Miedany, 2020). Este autor indica que a análise do FRAX pode estar associada a outras avaliações, como alterações microestruturais em exames de imagem.

1.1.4 Alterações na mandíbula e na maxila pela osteoporose

A osteoporose está relacionada ao metabolismo ósseo alterando a microarquitetura dos ósseos, incluindo os ossos da face (Barngkgei et al., 2015), e, uma vez que a osteoporose provoca alterações no formato das vértebras e no colo femoral, é de se esperar que existam alterações morfológicas também na mandíbula (Kanis et al., 2008, Dutra et al., 2006).

Diversos achados odontológicos se mostraram estar relacionados com a baixa DMO da coluna e do quadril, muitos destes podendo ser visualizados em exames de imagem. Na literatura foram descritos primeiramente os achados em radiografia panorâmica e em radiografias intrabucais, como a reabsorção do osso alveolar, a perda dentária, a própria DMO mandibular, a espessura da lâmina dura e a espessura da cortical da mandíbula (Vlasiadis et al., 2007).

Segundo Calciolari et al. (2016), a maxila, por ter mais osso trabecular em relação à mandíbula, poderia apresentar uma DMO mais semelhante à DMO da coluna. No entanto, a mandíbula tem mais referenciais anatômicos que possibilitam a padronização das avaliações, como, por exemplo, o forame mentual. Diversos estudos se voltaram, então, para a qualidade e espessura da cortical na mandíbula, que acompanha a atividade reabsortiva da osteoporose, com diminuição da sua espessura e tornando-se mais porosa (Sindeaux et al. 2014, Alman et al. 2012, Horner et al. 2010, Leite et al. 2010, Nackaerts et al. 2008, Taguchi et al. 2004).

Quanto à TCFC, estudos que utilizaram a imagem tomográfica também comprovaram alterações na mandíbula em pacientes com baixa DMO verificada por meio de densitometria (Slaidina et al., 2022, Aliaga et al., 2020; Bayrak et al., 2020; Hayashi et al.,2020; Nakamoto et al., 2020; Yeung & Mozos, 2020; Kato et al., 2019; Alkhader et al., 2018; Brasileiro et al.,2017; Barngkgei et al., 2016; Koh & Kim, 2011; Marandi et al., 2010).

Em um estudo prospectivo e longitudinal com 10 anos de acompanhamento, que avaliou radiografias panorâmicas, os resultados revelaram significativo risco relativo de fratura em pacientes com FRAX acima de 15% e cortical óssea mandibular com aspecto de erosão severa (Jonasson et al., 2018).

Outro estudo realizado com homens e mulheres entre 40 e 89 anos avaliou 422 radiografias panorâmicas e correlacionou doença periodontal, espessura da cortical mandibular e FRAX. Os resultados concluíram que o FRAX junto à radiografias que apresentavam aspecto de doença periodontal avançada e a presença de erosão da cortical óssea mandibular podem ser ferramentas para o cirurgião-dentista predizer o risco individual de fratura osteoporótica em mulheres (Kalinowski et al. 2019).

Um estudo coorte que avaliou mulheres de 1980 a 2002 observou que o aumento do espaçamento trabecular na mandíbula em radiografias panorâmicas e o FRAX acima de 15% estavam associados a maior risco de futura fratura. O FRAX acima de 15% sem avaliação de DMO é um preditor efetivo de fratura e o espaçamento do trabeculado ósseo foi um fator adicional ao resultado, sendo que juntos, FRAX e o espaçamento do trabeculado ósseo podem predizer fraturas maiores por osteoporose de forma semelhante à correlação entre FRAX e a baixa DMO (Sundh et al. 2017).

Com essa relação verificada, estes exames odontológicos surgem como instrumentos auxiliares na identificação da osteoporose e o cirurgião-dentista passa a ter um papel importante para o rastreamento de indivíduos com alto risco de fratura. A crescente demanda por exames tomográficos pelos cirurgiões-dentistas direcionou estudos para a aplicação dos índices radiomorfométricos na imagem tomográfica. Diferentemente da radiografia convencional, a tomografia não apresenta sobreposição de estruturas e distorções geométricas. No entanto, não foram encontrados estudos que analisassem a cortical óssea mandibular e o trabeculado ósseo em TCFC para identificação de indivíduos com osteoporose e alto risco de fratura analisados por DXA e a ferramenta FRAX.

1.1.5 Índices Radiomorfométricos

Os índices radiomorfométricos são fundamentados em osso cortical. Por serem mais facilmente visualizadas em radiografias do que o osso trabecular, as alterações em cortical óssea são mais utilizadas como parâmetro nos estudos. Portanto, diversos índices mandibulares foram utilizados para discriminar indivíduos com e sem osteoporose, levando em consideração, em sua maioria, a espessura da cortical

mandibular (ECM) e a integridade da borda inferior da mandíbula (Khojastehpour et al., 2011; Leite et al., 2010; Vlasiadis et al 2007; Dutra et al., 2005; Taguchi et al., 1995; Klemetti et al.,1994).

A ECM é uma avaliação quantitativa da cortical mandibular realizada na região de forame mentual. Para a realização da medida na radiografia panorâmica, o forame mentual é identificado e uma linha perpendicular ao forame e tangente à borda inferior da mandíbula é traçada (Figura 3). A medida da cortical é, então, realizada neste ponto. (Taguchi et al., 1995).

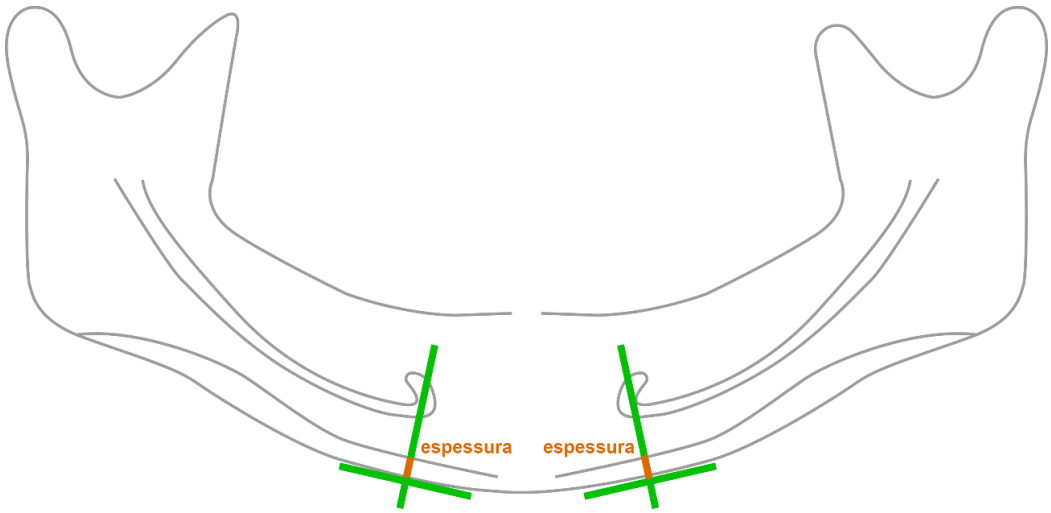

Figura 3 – Representação esquemática de mandíbula com linha perpendicular ao forame e linha tangente à borda inferior da mandíbula para cálculo da espessura da cortical inferior. Taguchi et. al. 1995 modificado. Fonte: elaboração própria

Para Devlin & Horner (2002), uma cortical mandibular menor que 3mm pode predizer uma baixa DMO. No entanto, a mensuração da ECM em radiografias panorâmicas pode ser um procedimento trabalhoso por necessitar de um paquímetro de precisão ou de um programa de computador para a mensuração na imagem digital (Lee et al., 2005).

Apesar de diversos autores defenderem a radiografia panorâmica como instrumento auxiliar no diagnóstico da osteoporose, a eficácia do exame para detectar

osteoporose na radiografia panorâmica é de baixa a moderada, segundo uma revisão sistemática. Neste estudo, os autores afirmam que radiografia panorâmica, por ser uma projeção bidimensional, apresenta limitações para realização de mensurações lineares devido à distorção geométrica intrínseca ao exame (Calciolari et al. 2015).

1.1.6 Tomografia computadorizada de feixe cônico (TCFC)

A TCFC consiste na aquisição de imagens volumétricas baseada na técnica de emissão de raios X em formato cônico para um detector de raios X. O paciente realiza o exame sentado e o aparelho faz um giro de 360° ao redor da cabeça do paciente. A cada grau, é gerada uma imagem base que se assemelha à imagem adquirida em uma telerradiografia. As imagens são depois reconstruídas em um volume em 3D por meio de programa apropriado instalado no computador ligado ao tomógrafo (De Vos et al. 2009; Arai et al., 1999).

Desde a sua introdução no mercado, há mais de duas décadas, a TCFC vem sendo largamente utilizada na odontologia, com diversas indicações para avaliação do complexo maxilofacial, superando algumas limitações relacionadas à sobreposição de imagem e distorções inerentes aos exames bidimensionais. Já foram catalogados no mercado 279 diferentes equipamentos de TCFC desde o seu surgimento (Gaêta-Araújo et al., 2020). A TCFC já pode ser considerada, portanto, como uma ferramenta imprescindível para várias tarefas diagnósticas e auxílio no planejamento do tratamento (Jaju et al. 2014).

Com a crescente utilização da TCFC, principalmente no planejamento para implantes em indivíduos idosos, que são considerados como um grupo de risco para osteoporose, torna-se necessário verificar se a TCFC, comumente indicada nos

planejamentos odontológicos, pode auxiliar na identificação da doença e de indivíduos com alto risco de fratura, pelas análises dos ossos cortical e trabecular.

1.1.7 Índices Radiomorfométricos em TCFC e correlações com baixa DMO

Baseando-se em estudos em radiografias panorâmicas, muitos métodos de avaliação na TCFC estão sendo propostos para o diagnóstico e acompanhamento das mudanças no tecido ósseo como preditor da osteoporose (Koh & Kim, 2011; Gomes et al., 2014; Alonso et al., 2016; Mostafa et al., 2016).

Koh & Kim (2011) avaliaram 42 mulheres na pós-menopausa, sendo 21 mulheres com osteoporose e 21 mulheres sem osteoporose. Cada paciente teve sua DMO avaliada por DXA da coluna (L1 e L3) e do fêmur, seguindo a classificação de T-score proposta pela Organização Mundial de Saúde (WHO, 1994). A região de forame mentual esquerdo foi escaneada utilizando-se o aparelho PSR-9000NTM Dental CT System (Asahi Roentgen Ind Co Ltd, Kyoto, Japan) com 80 kV, 10mA, 30 segundos de tempo de rotação, e as imagens foram posteriormente reconstruídas no software OnDemand3D. Neste estudo, os autores avaliaram os seguintes índices em corte coronal.

- CTI(S) - Índice Mandibular Tomográfico Superior: sendo a razão entre a ECM e a distância da margem superior do forame mentual até a borda inferior da mandíbula.
- CTI(I) – Índice Mandibular Tomográfico Inferior: razão entre a ECM e a distância da margem inferior do forame mentual até a borda inferior da mandíbula.
- CTMI – Índice Mentual Tomográfico: consistia na espessura da cortical mandibular.

- CTCI Índice Cortical Tomográfico: classificação da aparência da cortical mandibular em três tipos:
    - Tipo 1: cortical íntegra e contínua
    - Tipo 2: a margem endosteal apresenta defeitos semilunares ou uma ou duas camadas de resíduos do endósteo.
    - Tipo 3: a cortical apresenta mais de três camadas de resíduos do endósteo e é claramente porosa.

Os resultados mostraram diferença significante entre os grupos de mulheres com e sem osteoporose para os CTI(S) e CTI(I) (P<0,05). No entanto, não houve correlação entre os dois grupos para o CTMI (P>0,05). Para o índice qualitativo CTCI houve diferença significante entre os grupos (P<0,05), ou seja, nesse estudo, os autores verificaram que os dois índices quantitativos (equivalentes ao índice panorâmico mandibular) na TCFC e o índice qualitativo, semelhante ao proposto para radiografias panorâmicas (Klemetti et al., 1994), podem ser ferramentas promissoras na identificação de mulheres na pós-menopausa com osteoporose.

Mostafa et al. (2016) realizaram um estudo com 50 mulheres na pós-menopausa com idade entre 55 e 70 anos. Baseado na DMO mensurada pelo exame de DXA, 25 foram classificadas com osteoporose e 25 classificadas normais ou grupo controle. Três índices radiomorfométricos foram analisados em imagens de TCFC. Os termos utilizados foram modificações da classificação para radiografias panorâmicas:

- *Computed Tomography Cortical Index* como Índice Mandibular Cortical:
    - Avaliação qualitativa da cortical mandibular realizada em corte sagital
- *Computed Tomography Mental Index* como Índice Mentual:

- Espessura da cortical mandibular na região de forame mentual. Utilizando corte coronal, a mensuração da espessura da cortical mandibular é realizada em linha tangente à linha traçada na base da mandíbula.

- *Computed Tomography Mandibular Index* como Índice Mandibular Panorâmico:
  - No corte coronal, é feita a média entre a espessura da cortical mandibular e a distância entre a cortical mandibular inferior e o centro do forame mentual.

Foram encontradas diferenças estatisticamente significativas entre o Índice Mandibular Cortical Tomográfico (IMCT) de mulheres com e sem osteoporose. A maior correlação negativa foi entre o IMCT e o DMO da coluna. Quanto maior o T-score, maior foi a probabilidade de o exame ser classificado como tipo 1 ou C1. Uma alta correlação positiva foi encontrada entre a ECM e o IMCT com o DMO da coluna ($p<0.001$)($r=0.463$), ($p<0.05$)($r=0.340$) respectivamente. Os autores sugerem a utilização dos índices radiomorfométricos avaliados por TCFC como ferramenta auxiliar para predizer pacientes com risco a fratura por osteoporose e indicador de necessidade de avaliação da DMO.

Güngör et al. (2016) avaliaram 90 pacientes por meio de TCFC correlacionando com quatro análises com a DMO: os índices radiomorfométricos, o valor de TC, a análise dos histogramas de densidade e a dimensão fractal. Segundo o exame de DXA realizado, dessas 90 pacientes, 31 eram do grupo controle, 33 tinham osteopenia e 26 tinham osteoporose. As imagens foram adquiridas pelo aparelho i-CAT (Imaging Sciences Internacional INc., Hatfield, PA, USA), com FOV de 130mmx100mm. Os parâmetros utilizados foram de 120kV e 18,9mA com 8,9 segundos de tempo de

rotação. As imagens foram trabalhadas no software i-CAT Vision (Imaging Sciences Internacional Inc.). Os índices radiomorfométricos utilizados foram baseados no estudo de Koh & Kim (2011). Os resultados mostraram correlação positiva entre a DMO da coluna e a integridade da cortical mandibular inferior (P ≤0,01), CTI(I) (P ≤0,01) e CTI(S) (P ≤0,01). Uma correlação positiva também foi detectada entre a DMO do colo do fêmur e CTMI (P ≤0,01).

Alonso et al. (2016) compararam a cortical óssea de 30 mulheres na pós-menopausa que realizaram exame de radiografia panorâmica digital, pelo aparelho Orthopantomograph OP100D (Instrumentarium Corp. Imaging Division, Tuusula, Finland) e TCFC, pelo aparelho iCAT (Imaging Sciences International, Inc. Hatfield, USA) com 120kVp e 3-8mA. A cortical mandibular inferior foi classificada em C1, C2 e C3, e os cortes transaxiais foram os cortes de escolha para análise na reconstrução das imagens tomográficas. A concordância de resultados entre a reconstrução panorâmica e a radiografia panorâmica foi de 65%, e a concordância de resultados entre os cortes transaxiais e a radiografia panorâmica foi de 56.7%. Ou seja, na maior parte dos resultados, os cortes transaxiais superestimaram a classificação. Nos cortes transaxiais, 96.6% das pacientes foram classificadas como C2 e C3, enquanto na panorâmica foram apenas 86,7%. Assim como no estudo de Gomes et al. (2014), não foi realizada a comparação dos dados com DXA, impedindo a avaliação do exame de TCFC para identificação de indivíduos com baixa DMO.

Um estudo realizado na Universidade Federal de Minas Gerais avaliou 48 mulheres entre 61 e 70 anos que foram pacientes no serviço de odontologia no período de 2014 a 2016 e que realizaram exame tomográfico da mandíbula por TCFC. Foram feitas mensurações da espessura da cortical mandibular em 4 regiões de interesse e os valores foram correlacionados com o DMO das pacientes por exame

DXA. Os resultados levaram a conclusão que a TCFC pode ser útil para identificar pacientes com baixa DMO em mulheres na pós-menopausa (Barra et al., 2021).

1.1.8 Dimensão Fractal (DF)

A DF calculada em radiografias panorâmicas e tomografias de feixe cônico tem sido proposta como ferramenta auxiliar na detecção da doença osteoporose. A análise fractal é aplicada em diversas áreas e também na odontologia, uma vez que o tecido ósseo trabecular é uma geometria complexa composta por trabéculas e diferentes espaçamentos entre elas. (Backes et al, 2005, Sanchez et al., 2011; Franciotti et al. 2020; Faria et al. 2021).

A DF é um método matemático para descrever e analisar estruturas com padrões complexos, sendo uma mensuração quantitativa de uma imagem complexa. Este cálculo avalia o nível de irregularidades de formas e objetos, sendo seu valor diretamente proporcional à sua complexidade (Backes & Bruno, 2005). A arquitetura óssea é alterada na presença da osteoporose, pois ocorre a diminuição da espessura e o número de trabéculas ósseas e o espaçamento entre as trabéculas também é aumentado. Assim sendo, a atenuação da radiação X pelo osso é alterada e, portanto, a densidade e o padrão da imagem adquirida também são alterados (Chen et al.; 2018, Bachtler et al. 2020). O osso trabecular tem um padrão de ramificação que apresenta propriedades fractais tais como autossimilaridade e falta de escala bem definida (Figura 4).

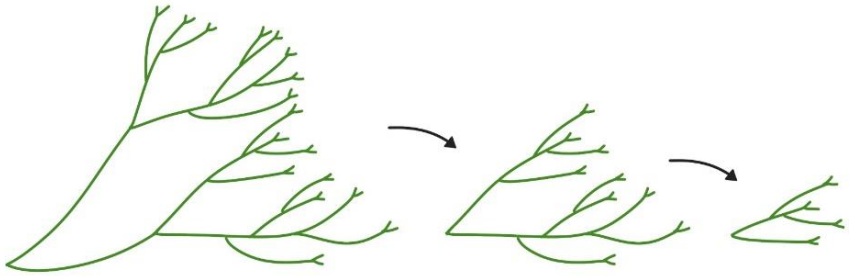

Figura 4 – Representação esquemática de um padrão de autossimilaridade. Fonte: elaboração própria.

Devido a este fenômeno, a aplicação da geometria fractal e a medição da DF podem ser usadas para determinar a complexidade e estrutura trabecular do osso. A aplicabilidade e a relevância da geometria fractal na análise de imagens são justificadas pelo fato de que a autossimilaridade pode ser verificada com uma resolução finita.

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2. CAPÍTULO 2 – OBJETIVOS, PACIENTES E MÉTODOS

2.1 OBJETIVOS

2.1.1 Objetivo geral

O objetivo geral desse estudo foi avaliar a cortical inferior da mandíbula e o trabeculado ósseo em exames de TCFC de mulheres na pós-menopausa e correlacionar com o resultado da análise da DMO (pelo exame de DXA) e o risco de fratura analisado pela ferramenta FRAX.

2.1.2 Objetivos específicos

- Avaliar a relação entre a análise da cortical inferior da mandíbula e a densitometria óssea de mulheres na pós-menopausa, com e sem osteoporose (capítulo 3 – artigo A: de Castro et al. 2020);
- Avaliar a acurácia da análise da cortical mandibular para identificar mulheres na pós-menopausa com osteoporose (capítulo 3 – artigo A: de Castro et al. 2020)
- Avaliar a relação entre medidas trabeculares da mandíbula e da coluna vertebral (análise da dimensão fractal) e a densitometria óssea de mulheres na pós-menopausa, com e sem osteoporose (capítulo 3 – artigo B: Carvalho et al. 2022);
- Avaliar a acurácia da análise de DF para identificar mulheres na pós-menopausa com osteoporose (capítulo 3 – artigo B: Carvalho et al. 2022);
- Avaliar a relação entre a espessura da cortical mandibular e a avaliação do risco de fratura pelo FRAX (capítulo 4- artigo C).
- Avaliar a acurácia destas medidas corticais para predizer o risco de fratura pelo FRAX, tendo como ponto de corte o risco igual ou maior que 3% para o quadril

e de 15% para uma fratura maior conforme estabelecido na literatura brasileira (capítulo 4 – artigo C).

2.2 PACIENTES E MÉTODOS

2.2.1 Pacientes

Inicialmente, pacientes com DMO normal e com osteoporose, de acordo com o exame de DXA da coluna lombar (L1-L4) e do fêmur proximal (colo femoral e fêmur total) foram selecionados do banco de dados do Serviço de Densitometria Óssea do Hospital Universitário de Brasília (HUB). Os exames selecionados deveriam ser de mulheres na pós-menopausa acima de 45 anos. Participaram deste estudo, 103 mulheres na pós-menopausa que tinham feito o exame de densitometria óssea da coluna lombar (L1-L4) e do fêmur proximal (colo femoral e fêmur total) no Centro de Radiologia Médica do Hospital Universitário de Brasília (HUB), e que tinham indicação de realizar o exame de tomografia computadorizada de feixe cônico

2.2.2 Critérios de inclusão

- Mulheres na pós-menopausa com DMO normal ou com osteoporose, segundo os resultados da densitometria óssea.
- Mulheres acima de 45 anos de idade.
- Pacientes com indicação de tomografia computadorizada de feixe cônico da mandíbula.

- Pacientes de acordo com o protocolo e assinar o termo de consentimento livre e esclarecido (apêndice 1).

2.2.3 Critérios de exclusão

- Pacientes com doenças osteometabólicas.
- Pacientes em uso de glicocorticóides ou outras medicações associadas à redução da massa óssea.
- Pacientes com diagnóstico de doenças causadoras de osteoporose secundária.

Vale ressaltar que o presente estudo selecionou apenas mulheres com diagnóstico densitométrico normal e com diagnóstico de osteoporose, excluindo da pesquisa pacientes com diagnóstico de osteopenia, minimizando a possibilidade de erros devido a valores limítrofes.

2.2.4 Procedimentos para coleta e análise dos dados

De acordo com os resultados dos exames de DXA, as pacientes com diagnóstico de osteoporose (avaliação em coluna lombar ou fêmur) e as com diagnóstico densitométrico normal em ambos os sítios ósseos foram convidadas a participar do estudo via ligação telefônica, sendo então encaminhadas para avaliação clínica na Unidade de Saúde Bucal do HUB. Inicialmente, um exame clínico foi feito por um aluno de iniciação científica do último ano do curso de Odontologia, seguindo o protocolo clínico da Unidade de Saúde Bucal. Pacientes parcialmente edêntulas ou totalmente edêntulas com indicação de TCFC para planejamento de implantes realizaram o exame no Centro de Radiologia Odontológica da Unidade de Saúde

Bucal. Todas as pacientes com necessidades de tratamentos odontológicos foram encaminhadas à clínica de graduação ou ao Centro de Especialidades Odontológicas do HUB para tratamento.

Os exames de DXA e TCFC não poderiam ser feitos em períodos distintos. Portanto, optou-se por uma diferença máxima de tempo de três meses entre os dois exames.

Esse estudo foi avaliado e aprovado pelo Comitê de Ética e Pesquisa em Seres Humanos da Universidade de Brasília (HUB), de CAAE número 47725815.1.3001.553.

2.2.5 Análise da DMO

Os exames de densitometria óssea da coluna lombar (L1-L4) e do fêmur proximal foram realizados pelo mesmo técnico no aparelho Lunar DPX NT (GE Healthcare, Madison, Wi, EUA). Os valores de densidade mineral óssea foram classificados como normal (T-score ≥ -1,0), osteopenia (Tscore entre -1,0 e -2,5), e osteoporose (Tscore ≤ -2,5), de acordo com os critérios definidos pela Organização Mundial de Saúde (WHO, 1994). A osteoporose foi definida quando o T-Score era inferior ou igual a -2,5 na coluna lombar ou fêmur. Os coeficientes de variação dos exames densitométricos da coluna lombar e do fêmur foram 1,0% e 1,2%, respectivamente.

Figura 5 – Fotografia do aparelho para densitometria óssea por DXA Lunar DPX NT localizado no Serviço de Densitometria Óssea do Hospital Universitário de Brasília.

2.2.6 Análise dos exames de TCFC

Os exames de TCFC foram realizados em aparelho i-CAT Classic (Imaging Sciences International, Inc., PA, EUA) presente na Unidade de Saúde Bucal do HUB, pelo mesmo operador. Para a aquisição dos exames, foram utilizados os seguintes parâmetros: tamanho de voxel de 0,25mm, 120kVp, 5mA, tempo de escaneamento de 26,9 segundos e o campo de visão personalizado, com o objetivo de abranger a mandíbula, incluindo a cabeça da mandíbula e o osso hioide. As imagens foram

analisadas utilizando o programa fornecido pelo fabricante do equipamento Xoran 3.1.62 (Xoran Technologies, Ann Arbor, Mich, EUA).

Figura 6 – Fotografia do aparelho i-CAT Classic presente na Unidade de Saúde Bucal do HUB. Fonte: elaboração própria

De cada escaneamento, foi realizada a reconstrução panorâmica e os cortes transaxiais. Para a obtenção destes cortes, seguiu-se a seguinte padronização (Figura 7):

1. Na tela de reconstruções multiplanares (MPR), a base da mandíbula foi alinhada no corte coronal (Figura 7A). Um filtro "*sharpen low 3x3*" foi aplicado nas imagens para avaliação.
2. Na mesma tela anterior, porém agora no corte axial, o ramo mandibular foi alinhado ao cursor (Figura 7B).

3. A espessura do corte sagital nesta tela foi ajustada em 75,00mm para o melhor alinhamento do ponto mais inferior da sínfise mandibular com o ponto mais inferior do ângulo da mandíbula (Figura 7C)
4. No corte axial, na altura do terço médio das raízes dos dentes, quando presentes, foi traçada uma parábola, no centro do rebordo alveolar da mandíbula (Figura 7D). A partir desta parábola traçada com o cursor do computador foram obtidos os transaxiais (figuras 7F, 7G e 7H).

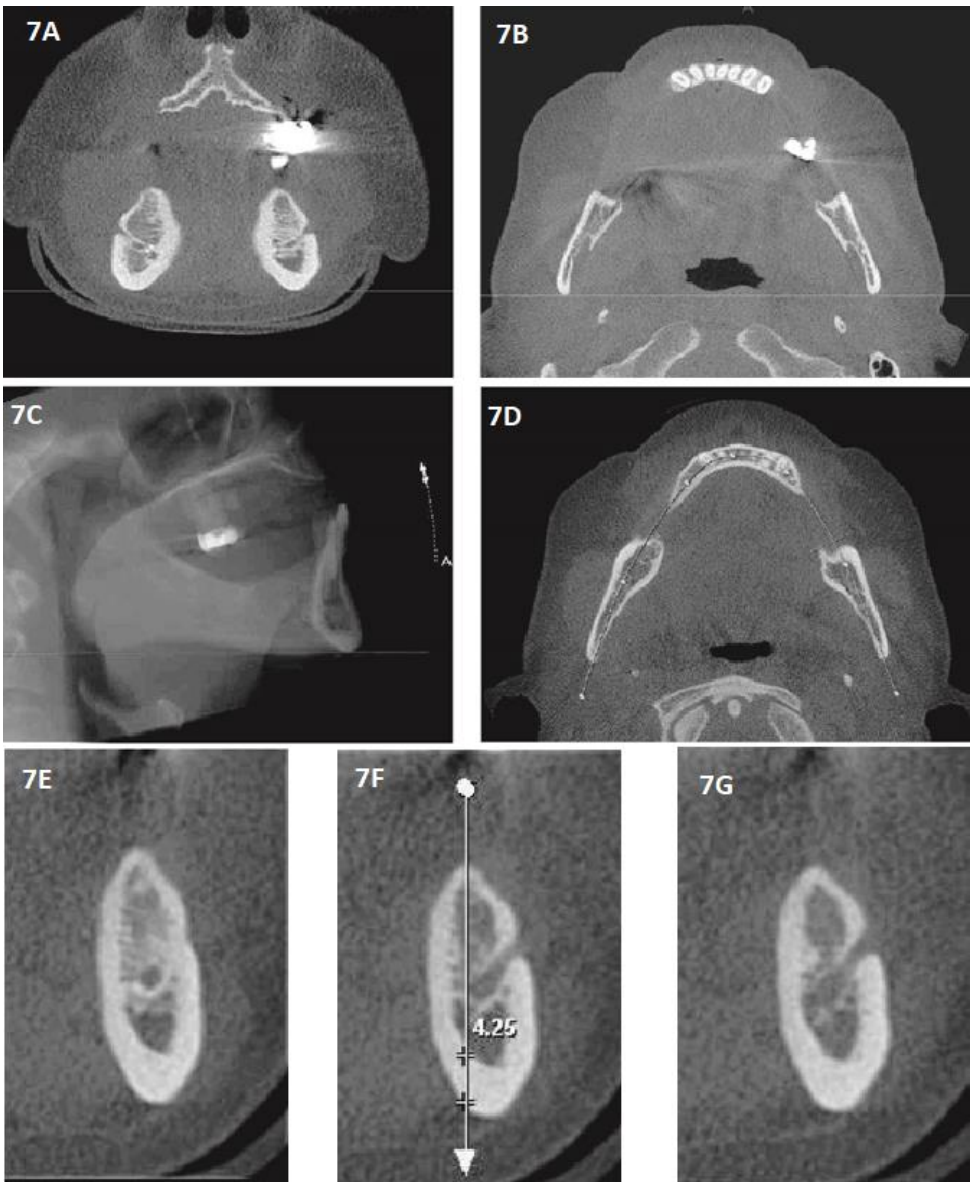

Figura 7 – Passos para obtenção e padronização dos cortes panorâmico e transaxiais. A – Alinhamento do ramo mandibular no corte coronal. B – alinhamento do ramo mandibular no corte axial. C – Alinhamento no corte sagital. D – Obtenção da parábola que define a

localização do corte panorâmico no corte axial. E a G – cortes transaxiais, sendo que na figura 1G está demonstrada como foi realizada a medida ECM.

Para a avaliação da dimensão fractal, foram escolhidas duas regiões de interesse (ROI), a segunda vértebra cervical (ROI-v) e a mandíbula (ROI-m). Os ROIs foram escolhidos de acordo com critérios descritos em outros estudos (Mostafa et al. 2016, Barngkei et al. 2015, Torres et al. 2011). Para a seleção destas ROIs, as imagens eram analisadas em reconstruções axiais, sagitais e coronais, em intervalos de cortes de 0,25mm para a ROI 1 e 1,25mm para a ROI 2, em monitor de LCD de alta resolução, em ambiente de baixa luminosidade. A avaliação inicial foi realizada com o programa fornecido pelo fabricante do equipamento Xoran 3.1.62 (Xoran Technologies, Ann Arbor, Mich, EUA).

A primeira região (ROI-v) foi adquirida da segunda vértebra cervical em corte coronal (Figura 8). O posicionamento foi calibrado a ponto de deixar o longo eixo, que passa pelo processo odontóide, perpendicular com o solo para todos os pacientes e centralizado no próprio processo odontóide em corte axial. Esta padronização para a seleção da ROI foi feita inicialmente na tela de reconstruções multiplanares (MPR), nos cortes sagital, axial e coronal. A segunda região de interesse (ROI-m) foi adquirida na mandíbula em um corte panorâmico tomográfico. Para melhorar o posicionamento e a curva que origina o corte panorâmico da tomografia, foi realizada a correção da inclinação no corte sagital para alinhar a maior porção de osso trabeculado. A localização da ROI-m foi anterior ao forame mentual, de forma a evitar o viés anatômico, ou seja, evitando a inclusão de estruturas anatômicas na região de interesse, tais como o forame mentual ou prolongamentos anteriores do canal mandibular (Figura 9). Ambos os ROIs selecionados foram de 40x40 pixels. A análise dos exames tomográficos pelos observadores foi realizada sem o conhecimento do

resultado da densitometria óssea. Estas imagens foram extraídas em formato DICOM e salvas em pastas separadas para cada paciente.

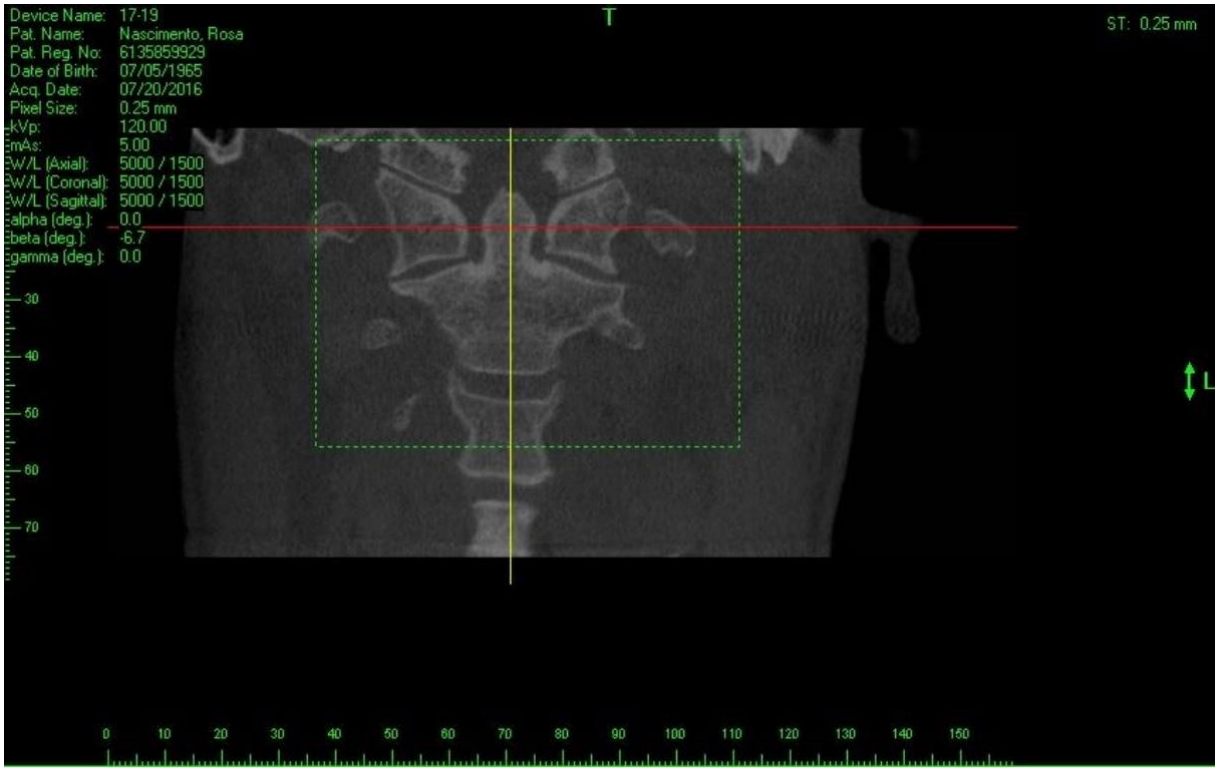

Figura 8 – Seleção de área referente à segunda vértebra cervical em corte coronal para a aquisição da ROI-v

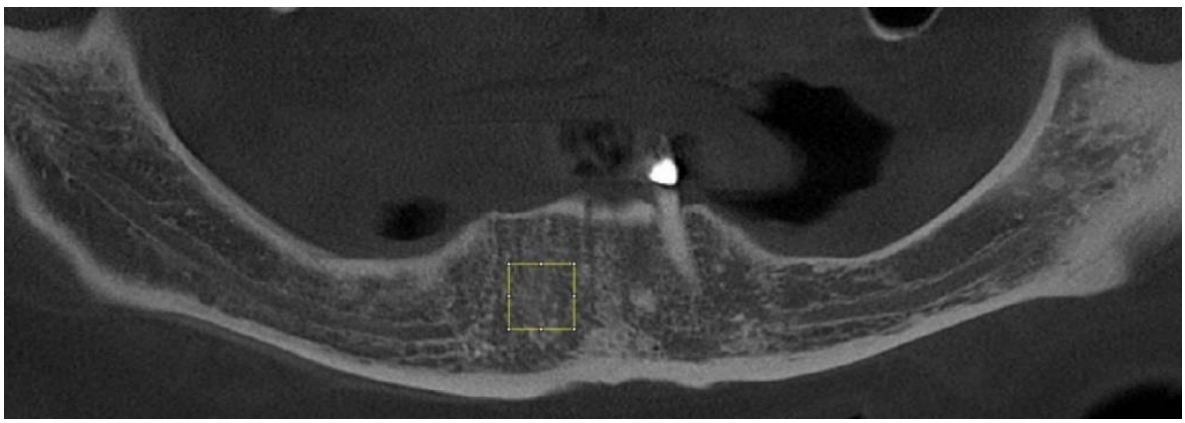

Figura 9 – Seleção de região na imagem panorâmica para a aquisição da ROI-m.

2.2.7 Análise do risco de Fratura

Para avaliação do risco de fratura, foi utilizado o FRAX considerando-se o ponto de corte proposto no FRAX brasileiro de 3% para o risco de fratura de quadril. Ou seja, foram consideradas mulheres com alto risco de fratura de quadril as que apresentassem um valor igual ou maior que 3% em 10 anos, pela ferramenta FRAX. Para o cálculo do FRAX, foi levado em conta:

- Gênero
- Peso
- Altura
- Fratura prévia
- Pais com fratura prévia de quadril
- Tabagismo atual
- Glicocorticoides
- Artrite reumatoide
- Osteoporose secundária
- Álcool 3 ou mais unidade/dia
- DMO do colo do fêmur.

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3. CAPÍTULO 3 – ARTIGOS PUBLICADOS

3.1 ARTIGO A:

de Castro JGK, Carvalho BF, de Melo NS, de Souza Figueiredo PT, Moreira-Mesquita CR, de Faria Vasconcelos K, Jacobs R, Leite AF. **A new cone-beam computed tomography-driven index for osteoporosis prediction.** Clin Oral Investig. 2020 Sep;24(9):3193-3202.

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3.1.1 ABSTRACT

Objective: To verify whether mandibular cortical analyses accurately distinguish postmenopausal women with normal Bone Mineral Density (BMD) from women with osteoporosis by means of a Cone-beam Computed Tomography (CBCT)-driven composite osteoporosis index (Three-dimensional Mandibular Osteoporosis Index - 3D MOI).

Material and methods: The comparison was performed between 52 women with normal BMD and 51 women with osteoporosis according to Dual-energy X-ray Absorptiometry (DXA) examination of the lumbar spine and hip. Mandibular cortical width (MCW) and cortical quality were evaluated on cross-sectional and panoramic

reconstructed images. ANOVA, ROC curves and accuracy measurements were used for statistical analyses, as well as a predictive model combining the quantitative and qualitative analyses and age.

Results: All CBCT-driven measurements presented good to moderate intra– and interobserver agreements. MCW values were significantly lower in women with osteoporosis. Postmenopausal women with osteoporosis were 8 times more likely to have the cortex classified as C3, and 2.4 times more likely to have MCW thinner than 2.75mm. The area under the ROC curve was 0.8 for the predictive model.

Conclusions: The newly developed 3D MOI enables distinguishing women with osteoporosis from those with normal BMD with good sensitivity and specificity.

Clinical relevance: Whenever a CBCT scan is performed for specific clinical indications, a 3D MOI may be performed to qualitatively and quantitatively assess the condition of the mandibular cortex. This may be surely helpful to assess the osteoporosis status in the ageing population and more specifically in peri- or postmenopausal women.

3.1.2 Keywords: Cone-beam computed tomography; osteoporosis; bone density; sensitivity and specificity

INTRODUCTION

Osteoporosis is a skeletal disease characterized by reduction of bone strength, which in turn creates a predisposition for minimal trauma fractures, also known as fragility fractures. This disease has a high economic and social impact on the worldwide population, due to the high costs related to the treatment of fragility fractures. Bone Mineral Density (BMD) and bone quality are the main determinants of bone strength, and generally the diagnosis of osteoporosis is based on BMD measurements by means of Dual-energy X-ray Absorptiometry (DXA) [1,2]. However, a low availability of DXA limits its routine use in population screening and efforts should be made to identify low BMD individuals, especially those who are at a higher risk of fractures. Therefore, different imaging exams have been studied as auxiliary tools for identifying low BMD individuals [3].

Several authors have evaluated mandibular cortex changes on dental panoramic radiographs of postmenopausal women, more specifically alterations in cortical porosity/erosion and thickness based on radiomorphometric indices [4-12]. Recently, some studies have analysed such alterations on Cone-Beam Computed Tomography (CBCT) due to its increasing use in dental practice, mainly for dental implant planning [13-17]. CBCT allows for three-dimensional visualization, consequently providing more information when compared to two-dimensional imaging modalities [18,19].

The applicability of different radiomorphometric indices used for identifying low BMD patients has been tested on CBCT scans, comparing postmenopausal women, and found lower values of these indices in osteoporotic women [13-17]. However, these studies had different methodologies and low sample sizes [13-17]. In fact, only one had tested the accuracy of a subjective qualitative index [17].

The main purpose of this study was to introduce a new composite CBCT-driven index with qualitative and quantitative analysis of the mandibular cortex for assessing osteoporosis (3D MOI), and to verify whether this composite tomographic index can accurately distinguish postmenopausal women with normal BMD from women with osteoporosis. The new index for assessing osteoporosis based on CBCT imaging was denoted as Three-dimensional Mandibular Osteoporosis Index (3D MOI). We hypothesized that the Mandibular Cortical Width (MCW) is smaller, and also that the mandibular cortex presents higher porosity/erosion on CBCT images of postmenopausal women with osteoporosis.

The combination of CBCT three-dimensional assessment of quantitative and qualitative appearance of mandibular cortical and patient's age might become a strong adjuvant diagnostic tool for referral of postmenopausal women at risk for osteoporosis.

3.1.3 METHODS

Participants

This retrospective study was based on the selection of CBCT images from postmenopausal women who also underwent DXA examinations for BMD testing. Importantly, the selected DXA and CBCT should have been performed in similar periods, with intervals of no more than three months between exams. Initially, 120 patients divided between those with normal BMD and those with osteoporosis according to lumbar and hip DXA were selected from the University Hospital database. All recruited participants were postmenopausal women aged >45 years, which had taken a good quality CBCT examination for dental purposes, such as implant planning. Postmenopausal women with any other metabolic bone disease except osteoporosis, or those who had taken medications affecting bone metabolism were excluded. The

Research Ethics Committee of the University of Brasilia approved this study according to protocol number CAAE 47725815.1.3001.553, and informed consents were obtained from all individuals. The declaration of Helsinki was followed in this investigation. Sample size had sufficient statistical power, with distribution *t* and *F* equivalent to 0.99 (effect size = 0.3 and type I errors = 0.05).

BMD assessment

The selected lumbar spine (L1-L4) and hip DXA scans were performed by the same technician using a Lunar DPX NT device (GE Healthcare, Madison, Wi, USA). The BMD values were classified as normal (T-Score ≥ -1.0), osteopenia (T-Score between -1.0 and -2.5), and osteoporosis (T-Score ≤ -2.5), according to the World Health Organization criteria [20]. Our diagnostic criteria for osteoporosis was a BMD T-Score of ≤ -2.5 at either the lumbar spine or the hip. Patients with osteopenia were not included in the study. The variation coefficients of the selected lumbar spine and hip measurements were 1% and 1.2%, respectively.

3D imaging by means of CBCT scanning

CBCT scans were taken using an I-CAT Classic device (Imaging Sciences International, Inc., PA, USA) with the following parameters: voxel size of 0.25mm, 120 kVp, 8mA, Field of View of 8 x 8cm, and a 40s scan time. Images were firstly analysed using the CBCT manufacturer software (Xoran 3.1.62, Xoran Technologies, Ann Arbor, Mich, USA).

Cross-sectional (CS) and panoramic images (PR) were reconstructed from all CBCT scans. A "sharpen low 3x3" filter was applied to the images for evaluation. The CS and PR were reconstructed by drawing the cutting curve on the centre of the axial images in which both mental foramina were most visible (Fig 1a) [17]. TIFF-format

images from all individuals were exported and analysed using the ImageJ software v1.47 (National Institutes of Health, Bethesda, MD, USA).

A new composite CBCT-driven osteoporosis index

A new composite CBCT-driven osteoporosis index (3D MOI) was established and included 3 measurements: two quantitative measures evaluating MCW on panoramic reconstruction images (3D MOI PR) and on cross-sectional images (3D MOI CS), and one qualitative measure assessing cortical bone quality (3D MOI CQ).

For measuring MCW, a line tangent to the inferior border of the mandible was drawn. Subsequently, a perpendicular line was drawn across this tangent line, passing through the centre of the mental foramen. At this point, the lower mandibular cortical was measured. Therefore, MCW in panoramic reconstructed images (3D MOI PR) was represented by the distance between the lower border of the mandible to the superior margin of the mandible cortex (Fig 1b). The panoramic image was reconstructed with a slice thickness of 10.25mm.

For the second measurement of the mandibular cortex, cross-sectional images were selected. A line tangent to the posterior border of the mental foramen was drawn and a measurement was performed at this point of the mandibular cortex (3D MOI CS; Fig 1c).

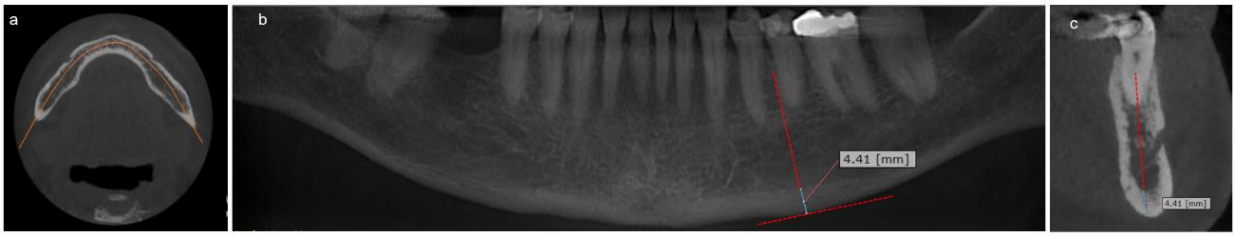

Fig 1. a. The CS and PR were reconstructed by drawing the cutting curve on the centre of the axial images in which both mental foramina were most visible. b. Three-dimensional Morphometric Index on Panoramic Reconstructed image (3D MOI PR) c. Three-dimensional morphometric index on Cross-Section (3D MOI CS).

The qualitative evaluation of the inferior cortex of the mandible was based on the classification initially proposed for dental panoramic radiographs [4], following the methodology applied by other authors on CBCT exams [13, 14, 22, 23]. The index was named three-dimensional mandibular osteoporosis index of cortical quality (3D MOI CQ). In the present study, cortical bone quality was evaluated below the mental foramen on both PR (Fig 2 – a, c and e) and CS images (Fig 2 – b, d and f), as follows:

C1: endosteal margin of the cortical being even and sharp (Fig 2a and Fig 2b).

C2: endosteal margin presenting semilunar defects (lacunar resorption) or appearing to form endosteal residues (Fig 2c and Fig 2d).

C3: cortical layer forming heavy endosteal cortical residues and being clearly porous (Fig 2e and Fig 2f).

The 3D MOI CQ was considered as positive when the cortex was classified as C2 and C3 on at least one CBCT reconstruction. (PR or CS).

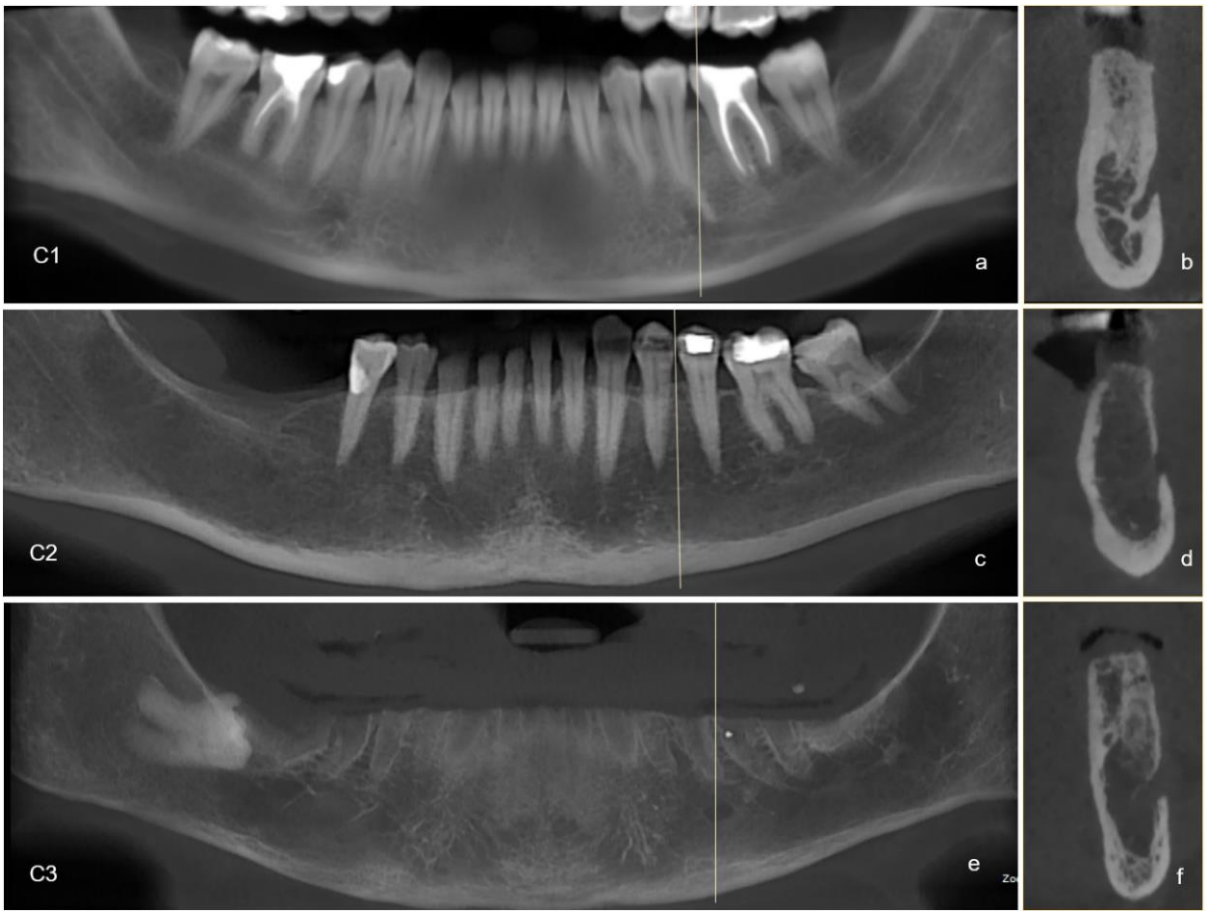

Fig 2. Scheme of the three-dimensional evaluation of the cortical quality (3D MOI CQ) using CBCT panoramic (a, c and e) and cross-sectional (b, d and f) reconstruction images and classified as: C1 (a and b), C2 (c and d) and C3 (e and f).

Images were analysed independently by two radiologists with more than ten years of experience with CBCT assessment, already calibrated for mandibular cortical analyses, and blinded for the DXA results, on a 25 inches high-resolution LCD display (2560 x 1440 pixels) in a calm and dim-lit environment. To calculate intraobserver reliability, one observer analysed the indices twice within one-week interval. For interobserver reliability, the results of the two observers were compared. For calculating the accuracy of the CBCT qualitative and quantitative measurements, we only considered the evaluation of the most experienced radiologist (first observer).

3.1.4 STATISTICAL ANALYSES

After checking the data for normal distribution data of CBCT indices, age, height, weight, and homoscedasticity (Shapiro-Wilk test and Cochran test), parametric analyses were performed. CBCT indices were compared between both groups using t test, analysis of variance (ANOVA) and least significant difference (LSD)-Fischer tests.

Sensitivity, specificity, positive and negative predictive values, and likelihood ratio of osteoporosis diagnosis in 3D MOI CQ were tested with dichotomous 2 x 2 tables. Testing of the proposed qualitative index considered two different categories of 3D MOI CQ: 1) women with eroded cortex (classifications C2 and C3) and women with non-eroded cortex (classification C1). Regarding DXA measurements, two groups were also considered, as follows: women with normal BMD (T-score ≥ -1.0) and women with osteoporosis (T-score ≥ -2.5) at either the lumbar spine or hip.

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off threshold of the 3D MOI PR and 3D MOI CS [24]. Accuracy measurements of these quantitative indices in the diagnosis of osteoporosis were calculated for optimal thresholds, and also considering the DXA groups.

The new 3D MOI index refers to cases in which the cortex was below the cut-off value according to the quantitative indexes (PR or CS) or were classified in C2 and C3, according to 3D MOI CQ (positive index = 1, negative index = 0)

Then, a predictive model combining the 3D MOI (qualitative and quantitative CBCT analyses) and age was built. This generalized linear model used a logit-link for binary data. A ROC curve analysis was applied to the predicted values of the model in order to find the coefficient of the intercept that maximizes specificity and sensitivity.

Every point on the line represents the sensitivity and specificity for a certain intercept value of the formula that results from the generalized linear model. The curve

enables to find that intercept value that maximizes specificity and sensitivity. It is the intercept that is linked to the point that is situated closest to the upper left corner of the graph.

The model generated the following formula:

Outcome=2.2194+2.4459*3D MOI index+0.0152*Age

This formula predicts osteoporosis if the outcome is positive, and predicts the absence of the disease when the outcome is negative.

Regarding intra- and interobserver agreements, the calculated values of 3D MOI PR and CS from the occasions in which each observer measured the CBCT scans were compared. This was done following a Bland & Altman's method [25]. For the qualitative index 3D MOI CQ, intra and interobserver agreement was tested by weighted Kappa test, and the interpretation was as follows: 0.00 =poor agreement, 0.00-0.2 = slight agreement, 0.21-0.4 = fair agreement, 0.41-0.60 = moderate agreement, 0.61-0.8 = substantial agreement and 0.81-1 = almost perfect agreement [26].

A p value less than 0.05 was considered statistically significant for all tests. Statistical analyses were performed using the Statistica 7.0 software (StatSoft, Inc, 2004, Statistica, version 7, Tulsa, OK, USA, www.statsoft.com) and Medcalc 16.8.4 (Medcalc Software bvba, Ostend, Belgium, https://medcalc.org, 2016).

3.1.5 RESULTS

From the 120 initially selected patients, 103 matched the inclusion criteria. According to the DXA, 52 women had normal BMD and 51 women had osteoporosis. Table 1 shows the comparison of descriptive data between the two studied groups. Differences were found for all variables between postmenopausal women with osteoporosis and those with a normal BMD, except for age. Both mandibular

measurements on CBCT scans were significantly different between osteoporotic and normal BMD group.

Table 1 – Comparison of mean values of descriptive data between postmenopausal women with normal BMD and osteoporosis.

Variables	Normal BMD Mean ± SD	Osteoporosis Mean ± SD	p-value
Age (years)	64.8 ± 9.8	63.9 ± 9.9	0.283
Height (cm)	157.7 ± 7.3	151.7 ± 6.3	<0.001*
Weight (kg)	73.2 ± 10.8	59.0 ± 10.7	<0.001*
BMD L1-L4 (g/cm^2)	1.2 ± 0.1	0.8 ± 0.1	<0.001*
BMD FN (g/cm^2)	1.0 ± 0.1	0.7 ± 0.1	<0.001*
BMD TH (g/cm^2)	1.1 ± 0.1	0.8 ± 0.1	<0.001*
3D MOI PR (mm)	3.1 ± 0.6	2.3 ± 0.8	<0.001*
3D MOI CS (mm)	3.1 ± 0.6	2.4 ± 0.8	<0.001*

BMD = Bone Mineral Density, FN = Femoral Neck, TH = Total hip, SD = standard deviation, L1 = first lumbar vertebra, L4 = fourth cervical vertebra, 3D MOI PR = tridimensional morphometric index on panoramic reconstruction images, 3D MOI CS = tridimensional morphometric index on cross-sectional images *p<0,05 (t test).

Reliability of 3D MOI

Intra and interobserver agreements

For the qualitative analysis, a moderate intraobserver agreement was found (kappa = 0.6). Figures 3a and 3b demonstrate that for both quantitative indices (3D MOI PR and 3D MOI CS, respectively), most of the measurements were within the limits of agreement. Regarding interobserver agreement, a fair agreement was found for the qualitative analysis (kappa = 0.4). Most of the measurements were also within the limits of agreement. 3D MOI PR (Fig 3c) presented less accurate results than 3D MOI CS (Fig 3d).

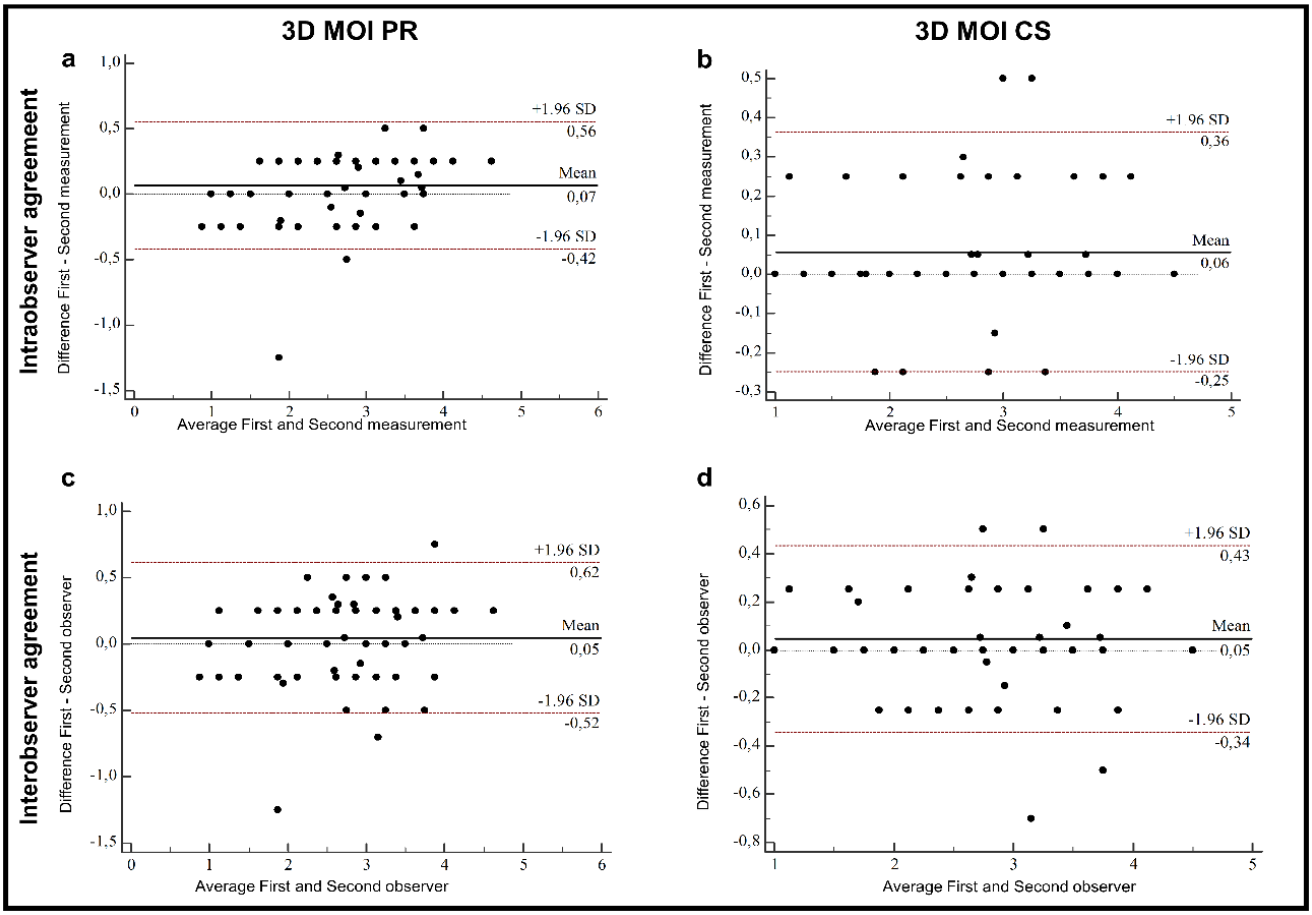

Fig 3. Bland-Altman plots showing good intra- and interobserver agreements for all the CBCT measurements. a. Intraobserver agreement for 3D MOI PR. b. Intraobserver agreement for 3D MOI CS. c. Interobserver agreement for 3D MOI PR. d. Interobserver agreement for 3D MOI CS.

Relationship between CBCT indices

A high correlation was found between quantitative 3D MOI PR and 3D MOI CS indices ($r = 0.946$, $p<0.001$). However, 3D MOI CS presented significantly higher values than 3D MOI PR (Fig 4). There was an association between quantitative and the qualitative index (Fig 5a and Fig 5b, respectively. No association was found between age and 3D MOI CQ, $p = 0.291$ (Fig 5c).

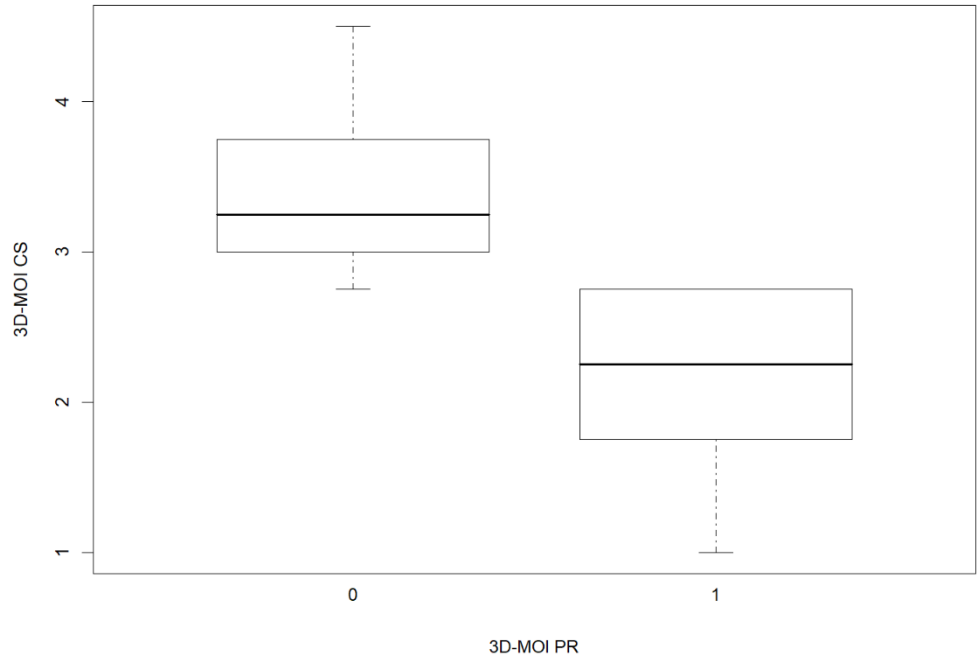

Fig 4. Box-plots comparing the two CBCT quantitative measurements. 3D MOI CS presented significantly higher values than 3D MOI PR.

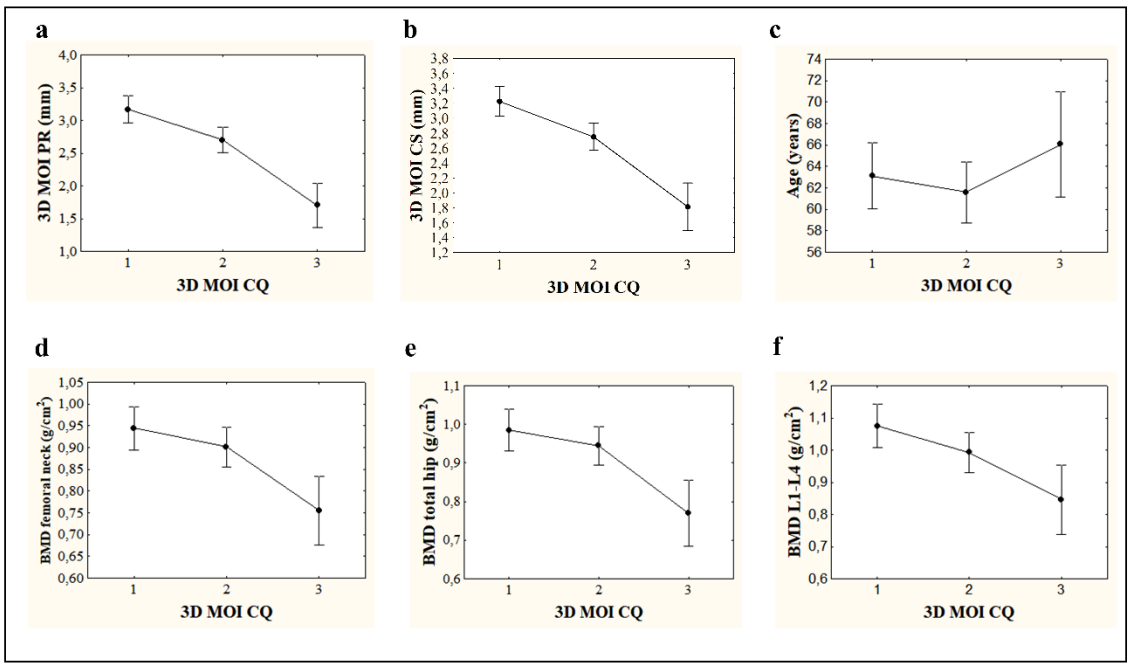

Fig 5. Significant association was found between 3D MOI PR and 3D MOI CQ. Women with C3 classification presented lower mandibular cortical width values on the CBCT images (a). Significant association was also found between 3D MOI CS and 3D MOI CQ (b). No association was found between age and 3D MOI CQ classification (c). Women with C3

classification in 3D MOI CQ presented lower mean values of bone mineral density at femoral neck (d), total hip (e), and lumbar spine (f).

Relationship between skeletal BMDs and CBCT driven variables (3D MOI)

Regarding 3D MOI PR, correlations were found between BMDs at the lumbar spine ($r=0.477$, $p<0.001$), femoral neck ($r=0.509$, $p<0.001$) and total hip ($r=0.513$, $p<0.001$). Correlations were also found for 3D MOI CS at the same three bone sites ($r=0.460$, $r=0.457$, $r=0.470$; $p<0.001$, respectively). Figures 5d, 5e and 5f show that there was an association between 3D MOI CQ and BMDs at the femoral neck, the total hip, and the lumbar spine, respectively. Postmenopausal women classified as C3 presented lower values of BMD at all three bone sites. On the other hand, higher BMDs values were found in postmenopausal women with a C1 classification of 3D MOI CQ.

Accuracy of CBCT indices for identifying women with osteoporosis

Table 2 demonstrates sensitivity, specificity, predictive values, likelihood ratios, and the areas under the curve of the CBCT indices regarding diagnosis of postmenopausal women with osteoporosis at the lumbar spine or proximal femur. For the quantitative CBCT measurements (3D MOI PR and 3D MOI CS), a cut-off value of 2.75mm was found.

Table 2 – Sensitivity, specificity, predictive values, likelihood ratios and areas under the *ROC* curves for identifying women with osteoporosis by CBCT indices

	3D MOI CQ	3D MOI PR (2.75mm)	3D MOI CS (2.75mm)	PREDICTIVE MODEL (3D MOI + AGE)
Sensitivity	54%	78%	76%	74.0%
Specificity	93%	67%	69%	80%
PPV	87%	70%	71%	79%
NPV	70%	76%	75%	76%
LR+	8.1	2.4	2.5	3.8
LR-	0.5	0.3	0.3	0.3
AUC	0.7	0.7	0.7	0.8

3D MOI = Tridimensional Mandibular Osteoporosis Index, PR = Panoramic Reconstruction, CS = Cross-sections, PPV = Positive Predictive Value, NPV = Negative Predictive Value, PPV = Positive Predictive Value, NPV = Negative Predictive Value, LR+ = Positive Likelihood Ratio, LR- = Negative Likelihood Ratio, AUC = Area Under the Curve

The predictive model that combines qualitative and quantitative CBCT measurements with age showed the highest AUC, with sensitivity and specificity values above 74.0%. Figure 6 demonstrates the ROC curve for the predictive model, and also the equation of this model.

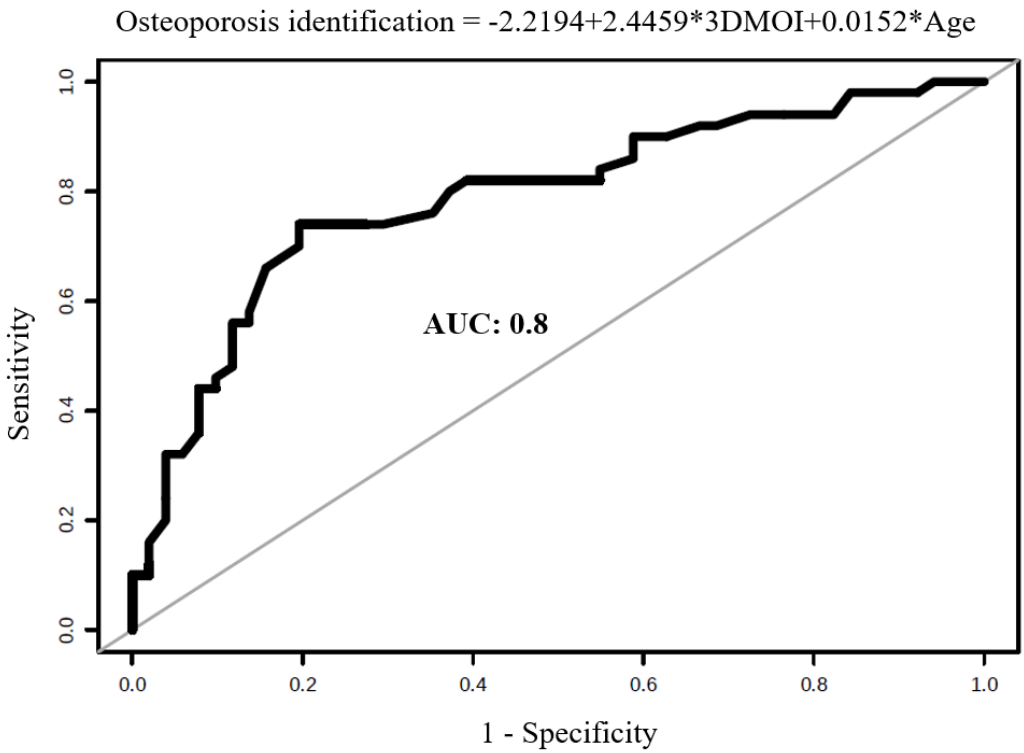

Fig 6. The predictive model for identifying postmenopausal women with osteoporosis combining 3D MOI (qualitative and quantitative analyses) and age. This model was built based on a ROC-curve analysis. The area under the *ROC* curve was 0.8. The formula of the model is shown on the upper part of the graph.

3.1.6 DISCUSSION

To the best of our knowledge, this is the first diagnostic test study that analysed the accuracy of both qualitative and quantitative indexes on CBCT for identifying low BMD patients, and presents a predictive model for identifying osteoporotic patients based on CBCT measurements and age. Significant differences between postmenopausal women with normal BMD and postmenopausal women with osteoporosis were found in MCW values measured on two different CBCT reconstruction images (panoramic and cross-sectional). These aforementioned measurements also presented a positive correlation with BMDs of the lumbar spine, femoral neck and total hip. Furthermore, an association was found between the visual analysis of the cortical quality and BMDs. The predictive model combining the three

CBCT measurements with age has demonstrated the highest area under the ROC curve (0.8). Accordingly, this model might be effective as an adjuvant tool for identifying low BMD postmenopausal women that underwent CBCT scans for dental purposes.

Few studies have evaluated radiomorphometric indices on CBCT, and their applicability is still being questioned [13-17, 21-23]. The CBCT indices are generally variations of the radiomorphometric indices evaluated on dental panoramic radiographs [6-12]. However, image acquisition is very different between these two imaging modalities, which precludes direct comparison of our results with the positive results found in most of the studies performed with dental panoramic radiographs.

Recent studies [13-17] have compared analyses of quantitative and qualitative cortical measurements on CBCT with DXA results at the lumbar spine or hip. In those studies, as well as in the present study, radiomorphometric indices assessed in CBCT were used to differentiate women with osteoporosis from women with normal BMD according to DXA results. Nevertheless, there are significant methodological differences between those studies and the present study.

Most of the previous studies did not fully analyse the reliability of the CBCT measurements [13-16]. One assessed only the intraobserver agreement [13]. Besides, some of them used a correlation coefficient of the measurements, which is not the most adequate method [13, 16]. Other methodologies [25,27] were proposed to evaluate the precision of quantitative measurements, such as those performed in the present study. Most of the measurements of MCW on both reconstructed images (3D MOI PR and 3D MOI CS) were within the limits of agreement, although higher precision was observed for 3D MOI CS.

Mean values of MCW were significantly lower in women with osteoporosis than in women with normal BMD according to DXA at all three bone sites (lumbar spine,

femoral neck and total hip). Our results are in line with the recent literature [14-16]. Only one study did not find significant differences in MCW between women with osteoporosis and women with normal BMD. Nevertheless, differently from the other studies, the quantitative CBCT index was measured on coronal images, and the results were compared only with DXA at the lumbar spine [13]. In the group with normal BMD (21 women), the mean MCW (±SD) was 3.22mm ± 0.87mm, and among women with osteoporosis (21 women) the mean MCW was 2.23mm ± 0.85mm [13]. The lack of statistical significance in this previous study was probably due to its small sample size, as well as to the large variance of the analysed data.

Regarding the qualitative index (3D MOI CQ), there was a higher frequency of C1 classification in women with normal BMD and a higher frequency of C3 classification in women with osteoporosis. Similar results were found in the literature [13,15,17]. As far as we are concerned, only one previous study evaluated the accuracy of measurements for screening postmenopausal women with low BMD, considering only the qualitative index. For such analysis on panoramic reconstructions of CBCT images, the reported sensitivity was 52.6%, the specificity was 62.5% for a slice thickness of 25mm [17]. These lower values of diagnostic accuracy measurements, when compared to our results, may be related to methodological differences, such as different evaluation method of osteoporosis status, and also differences in slice thickness of PR reconstruction. We calculated the accuracy in patients with osteoporosis (T-Score ≤ -2.5) and without osteoporosis (T-Score > -2.5) while the previous study has compared postmenopausal women with normal BMD (T-Score ≥ -1.0) with women with low bone mineral density (T-Score < -1.0) [17]. Our study not only used a subjective cortical analysis, but also showed by a predictive

model that the combination of both qualitative and quantitative analyses and age may increase the accuracy measurements.

It should be pointed out that the main advantage of the visual cortical analysis in the present study was the highest specificity (93.3%). On the other hand, the main shortcoming was related to the reliability of the qualitative index, especially when classifying the mandibular cortex as C2. Intra- and interobserver Kappa values varied from moderate to fair, respectively. The low reproducibility may be a limitation of the method itself and reinforces the importance of adding quantitative measurements for osteoporosis prediction. Therefore, based on the Osteodent study with panoramic radiographs, a predictive model combining quantitative and qualitative mandibular cortical analyses (3D MOI) on CBCT imaging with women`s age has been proposed in this study [7, 9].

The quantitative indices showed a tendency to present a better diagnostic outcome, expressed by higher values of areas under the ROC curves. For dental panoramic radiographs, some authors have demonstrated that MCW had better efficacy in identifying individuals with low BMD when compared to qualitative cortical mandibular index [28-30]. Concerning MCW on the radiographs, the authors found a cut-off point of 3mm as a parameter to referring patients for further medical investigation of osteoporosis [30]. In our study, the cut-off found for the CBCT examination was 2.75mm for both panoramic and cross-sectional CBCT images, resulting in sensitivity and specificity values close to or above 70%.

This retrospective study used a convenience sample based on an imaging and DXA database. Therefore, to match the inclusion criteria all the women should have undergone CBCT for dental purposes, and also lumbar and femoral DXA. Additionally, our reference standard was BMD according to DXA. The relationship between

mandibular bone changes and the risk of fractures still requires further investigation. This was the first diagnostic test study to assess the accuracy and precision of quantitative indices on CBCT, which precluded any comparison with previous studies. Our predictive model for osteoporosis should also be further investigated for other populations.

In conclusion, a composite CBCT-driven index (3D MOI) was established and demonstrated to be significantly different between postmenopausal women with normal BMD and those with osteoporosis. The 3D MOI may combine the advantages of a feasible and simple visual analysis of the mandibular cortex with higher specificity, with more precise and accurate quantitative measurements of the cortical width. In addition, the predictive model considered not only these CBCT measurements, but also the well-known risk factor for the disease which is the women`s age. According to our newly proposed index, elderly postmenopausal women undergoing CBCT for unrelated dental purposes should be referred for further medical investigation when presenting a mandibular cortex with C3 classification and a mandibular cortical width below 2.75mm.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The authors gratefully acknowledge financial support from Fundação de Apoio à Pesquisa do Distrito Federal– FAP-DF.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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3.2 ARTIGO B:

Carvalho BF, **de Castro JG**, de Melo NS, de Souza Figueiredo PT, Moreira-Mesquita CR, de Paula AP, Sindeaux R, Leite AF. **Fractal dimension analysis on CBCT scans for detecting low bone mineral density in postmenopausal women**. Imaging Sci Dent. 2022;52:e3.

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Received July 7, 2021; Revised October 19, 2021; Accepted October 18, 2021

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ABSTRACT

Purposes: To compare fractal dimension (FD) measured at two bone sites (second cervical vertebra and mandible) on cone-beam computed tomography (CBCT). The research question was whether FD could serve as an accessory tool to refer postmenopausal women to densitometric analysis. Therefore, reliability and the accuracy of FD were evaluated.

Materials and Methods: In total, 103 postmenopausal women were evaluated, of whom 52 had normal bone mineral density and 51 had osteoporosis, according to

dual X-ray absorptiometry of lumbar spine and hip. On the CBCT scans, two regions of interest were selected for FD analysis: one at the second cervical vertebra, and the other located at the mandible. The correlations between both measurements, intra- and interobserver agreements and the accuracy of the measurements were calculated. A p value less than 0.05 was considered statistically significant for all tests.

Results: FD mean values were significantly lower at the mandibular region of interest of osteoporotic patients when compared to individuals with normal bone mineral density. The areas under the curve were 0.644 (p=0.008) and 0.531 (p=0.720) for the mandibular and vertebral sites, respectively.

Conclusion: FD at the vertebral site could not be used as an adjuvant tool to refer women for osteoporosis investigation. Although FD differed between women with normal BMD and osteoporosis at the mandibular site, a low accuracy and reliability was found.

Key Words: Osteoporosis; Cone-Beam Computed Tomography; Fractals; Dual-Energy X-ray Absorptiometry.

3.2.1 **INTRODUCTION**

Osteoporosis is a common skeletal disease characterized by compromised bone strength that predisposes individuals to minimal trauma fractures, also known as fragility fractures. There are two main properties that relate to bone strength: Bone Mineral Density (BMD) and bone quality.[1] Osteoporosis is a major public health concern, due to the social and economic burden caused by the fragility fractures. This disease affects mostly the elderly population and postmenopausal women. The costs associated with the disease tend to rise with the ageing of the populations worldwide.[2,3] Hence, it is very important to identify low BMD individuals, and especially those who are at a higher risk of fractures.[4]

The diagnosis of osteoporosis is generally based on the measurement of BMD, which is routinely determined by Dual-Energy X-ray Absorptiometry (DXA). Even though DXA is considered to be the gold standard method for the diagnosis of osteoporosis, the exam is not widely available and its effectiveness is limited when evaluating altered bone quality.[4,5] Many patients with normal BMD or osteopenia, according to DXA, suffer from fragility fractures.[6] Therefore, auxiliary methods are necessary to identify microstructural bony changes.

One of the most important factors contributing to bone strength is its complex structure.[7] Some authors have stated that texture analysis and gray values of radiographic images may be related to bone microarchitecture.[8,9] Bone texture imaging parameters, including fractal dimension (FD) analysis of the femur and the vertebrae, may improve failure load prediction when added to BMD.[10–12] FD is a mathematical technique that allows the quantification of complex structures, which cannot be made by using conventional mathematics. This technique evaluates the level of irregularities and forms of objects. Its value is directly proportional to the image complexity.[13] Although several studies have tested FD on dental imaging modalities as a

complementary tool to identify low BMD individuals, most of the studies were based on two-dimensional examinations.[14-19]

Cone-beam computed tomography (CBCT) scans have become more popular in dental practice. The elderly population represent the largest risk group for osteoporosis and CBCT scans are often used for several reasons in these patients, mainly for planning implants, detecting pathology sites and locating retained teeth.[20,21] There are few up to date studies that have assessed CBCT indices and they have indicated the possibility of osteoporotic screening based on such imaging modality.[22-25] Only two recent studies have tested FD analysis on CBCT for identifying postmenopausal women with osteoporosis, in which controversial results were shown.[26,27] Nevertheless, such studies were substantially different in terms of methodology, had small samples and were only observational, which means that accuracy measurements were not established for the FD method.

The purpose of this study was to verify whether there were differences in mandibular and vertebral FD analyses on CBCT scans of postmenopausal women with normal BMD and osteoporosis.

3.2.2 MATERIALS AND METHODS

Initially, 150 patients with normal BMD or osteoporosis were selected from the database of the Bone Densitometry Service of the University Hospital of Brasilia. Of these patients, 103 were included in this study, since 47 were excluded due to being patients diagnosed with osteopenia. This exclusion criterion was chosen to prevent middle range results between normal and osteoporosis BMD. Out of the selected patients, 52 had normal BMD and 51 were diagnosed with osteoporosis according to lumbar and hip bone density by DXA. The participants were required to be postmenopausal women, aged over 45 years, to whom CBCT exams were indicated for implant planning purpose. Patients who were previously diagnosed with other metabolic bone disease, or those who had taken medications affecting bone metabolism were excluded. The sample was conveniently composed by partially or totally edentulous postmenopausal women, all of which had CBCT exam indication. DXA and CBCT were performed in similar period, within a maximum difference of three months between the exams. The study was approved by the local Institutional Review Board in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants included in the study received and signed and informed consent. The sample size had sufficient statistical power with distribution t and F equivalent to 0.99 (effect size = 0.3 and type I errors = 0.05).

BMD assessment

DXA of the lumbar spine (L1-L4) and hip were performed by the same operator using a Lunar DPX NT device (GE Healthcare, Madison, Wi, USA). BMD values for lumbar spine, femoral neck (FN) and total hip (TH) were classified as normal (T-score ≥ -1.0) and osteoporosis (T-score ≤ -2.5), according to the WHO criteria,[28] and the

patients were diagnosed with osteoporosis when one of the mentioned regions had the compatible T-score for such. Patients with osteopenia were not included in the study. The coefficients of variation of the selected lumbar spine and hip measurements were 1% and 1.2%, respectively.

CBCT scans

CBCT scans were acquired using an I-CAT Classic device (Imaging Sciences International, Inc., PA, USA) with the following parameters: voxel size of 0.25 mm, 120 kVp, 8 mA, field of view of 20 cm x 8 cm, and a 40 sec scan time.

The images were initially assessed by using the software supplied by the CBCT manufacturer (Xoran 3.1.62, Xoran Technologies, Ann Arbor, MI, USA). From all CBCT scans, two regions of interest (ROI) were selected. The ROIs were chosen according to the criteria proposed in previous studies,[26,29,30] in which different shapes and sizes were applied. Images were analyzed in the axial, sagittal and coronal sections with slices of 0.25 mm for the first ROI (ROI-v), which assessed the second cervical vertebra, and slices of 1.25 mm for the second ROI (ROI-m), which was selected in the mandible. After an interval of 1 week, the same image analyses were repeated to evaluate the intraobserver and interobserver agreements.

The ROI-v was acquired from the coronal view of the second cervical vertebra (C2). This ROI was selected by centering the C2, using the sagittal (Fig. 1A.), axial (Fig. 1B.), and coronal (Fig. 1C.) planes, so that a cross-marked its center.

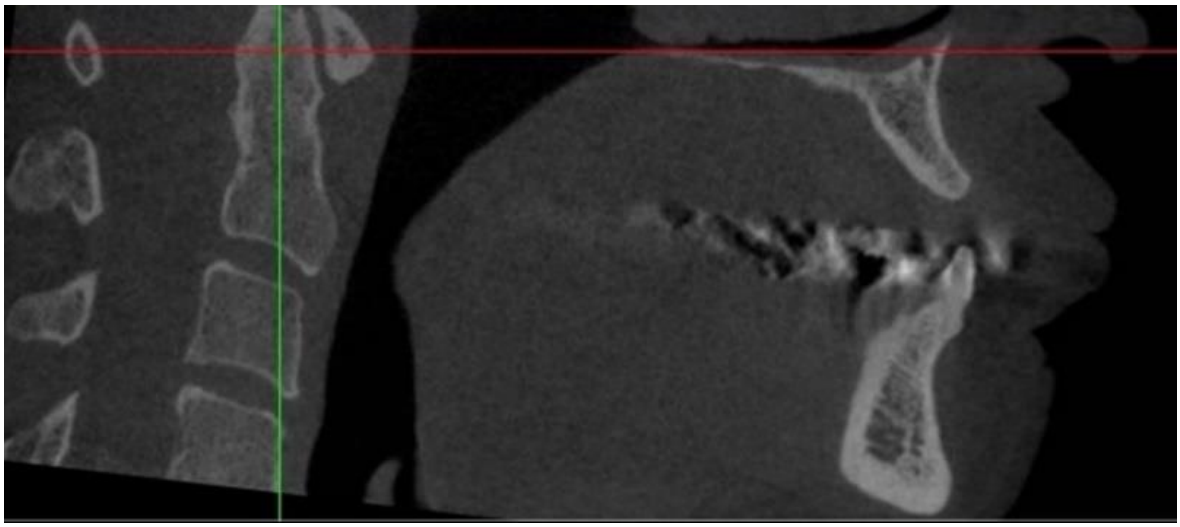


Fig. 1A.

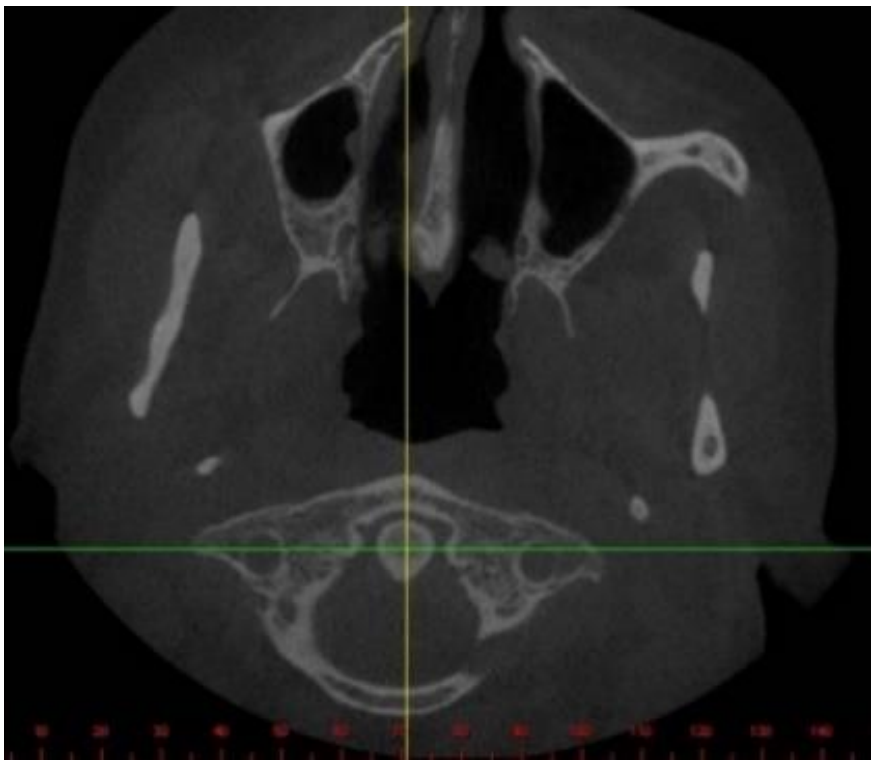


Fig. 1B

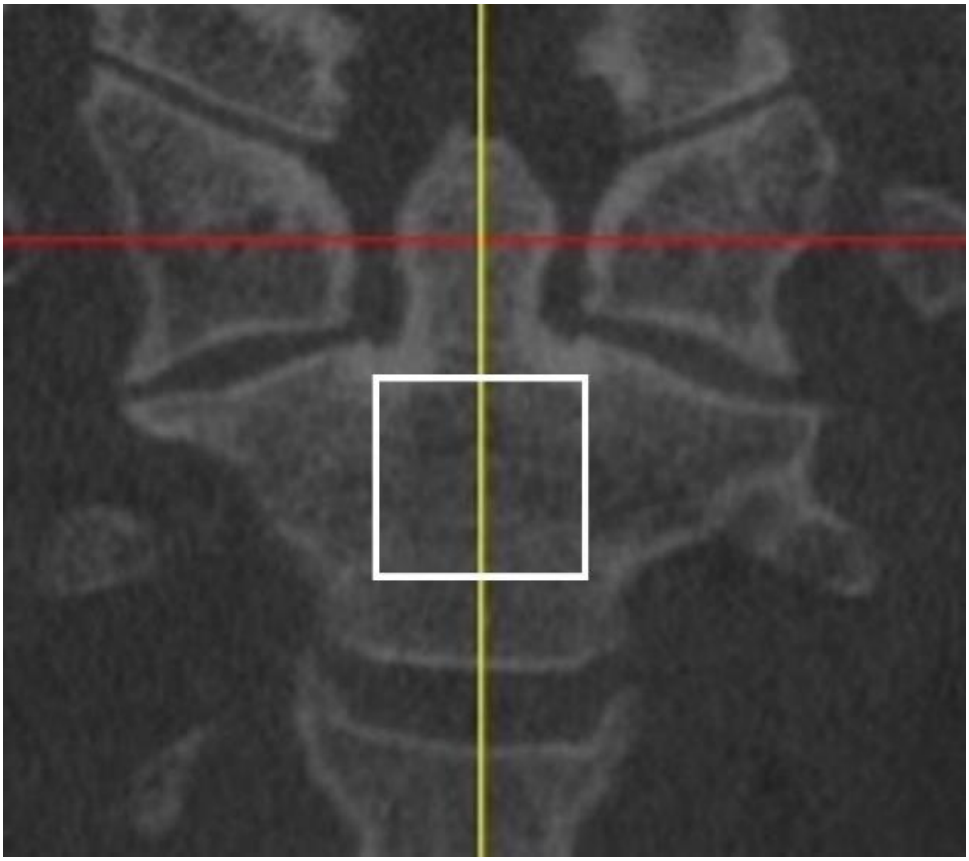


Fig. 1C.

Figure 1. Slices used for the assessment of the second cervical vertebra, as well as their positions and alignments. This ROI was standardized by calibrating the position of C2. A line was drawn passing through the dens in the sagittal plane (Fig. 1A.) and tilting it perpendicular to the computer screen. The most central point of the dens was located in both axial (Fig. 1B.) and coronal images (Fig. 1C.), so that a cross-marked its center.

The ROI-m selection started by creating a panoramic reconstruction image of the mandible. This ROI was then defined using the sagittal (Fig. 2A.), and the axial (Fig. 2B.) planes. The panoramic reconstruction image showed mostly trabecular bone, avoiding any cortical bone overlap (Fig. 2C.).

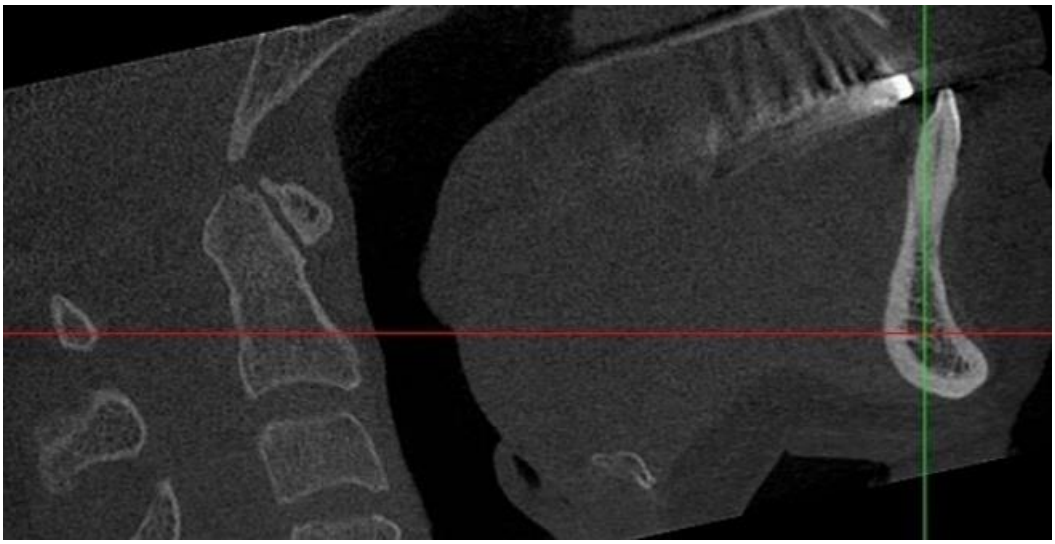


Fig. 2A.

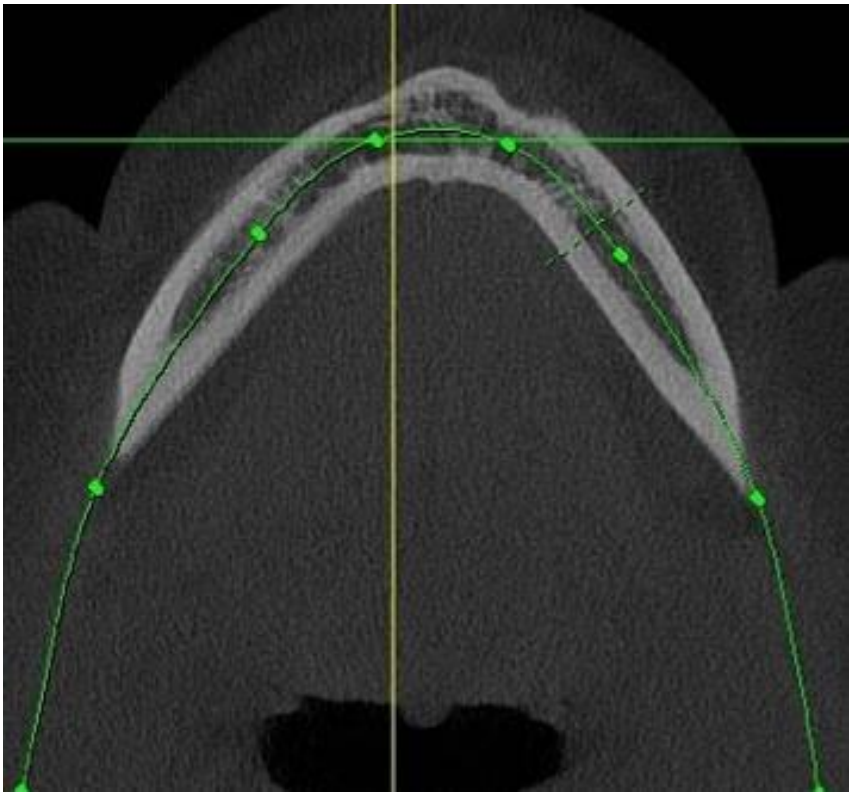


Fig.2B

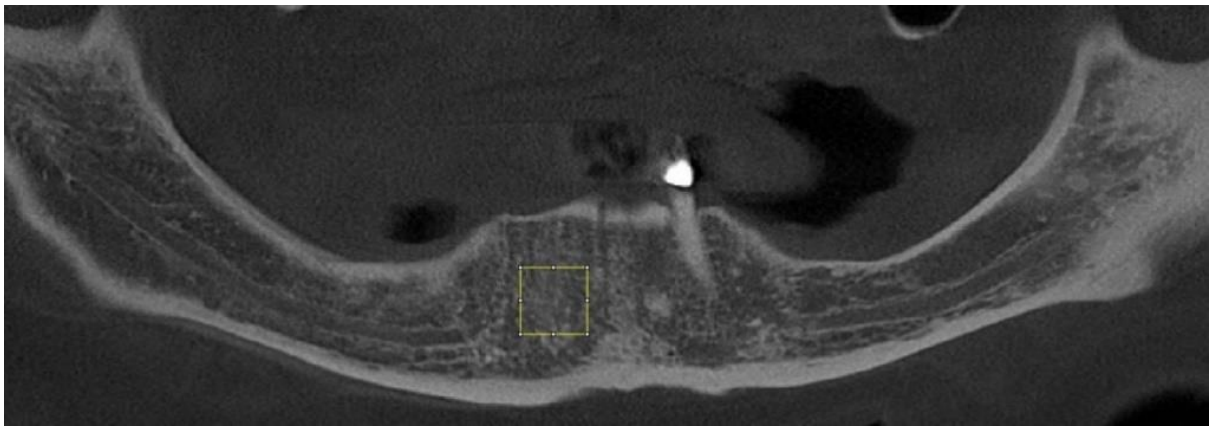


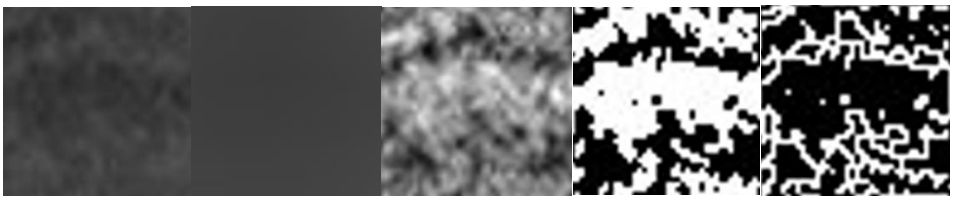
Fig. 2C.

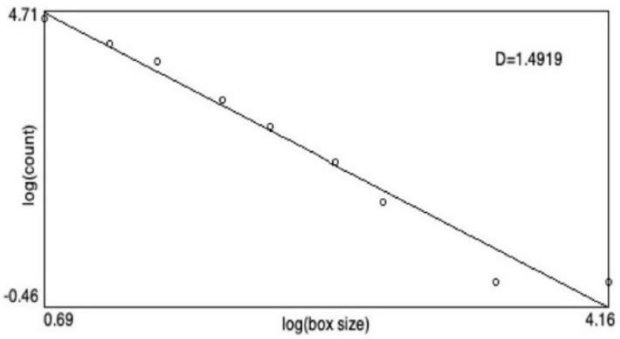
Figure 2. Images used for assessing the mandible, including their positions and alignments. In the sagittal view (Fig. 2A.) the mental foramen was tilted until it was also perpendicular to the computer screen. The cutting curve was drawn on the center of the axial image of the mandible (Fig. 2B.) in order to reconstruct the panoramic image (Fig. 2C.). The standardization aimed at showing mostly trabecular bone, avoiding any cortical bone overlap. The selected region of interest at the mandibular site measured 40 x 40 pixels (Fig. 2C. – square).

This ROI was selected at the right side of the mandible and was chosen to avoid anatomical interferences such as teeth, foramina, and the inferior alveolar canal. Another advantage of this position is that some patients with edentulous posterior regions are likely to have a lower bone volume due to physiological resorption. Both vertebral (Fig.1C.) and mandibular ROI (Fig. 2C.) measured 40x40 pixels.

The images were processed and analyzed with ImageJ, a public domain software (available at http://rsb.info.nih.gov/nih-image). FD was analyzed through a plugin for ImageJ called BoneJ, which uses the box counting method. Images were processed and FD calculation was based on the protocol that has been traditionally used in studies which assessed conventional radiographs[14–16] and was previously described by White & Rudolph in 1999.[32] This image processing was adapted to a CBCT imaging, considering its three-dimensional nature and according to previous studies.[16,17,32] Figure 4 illustrates such protocol applied to the selected ROIs, with the

following steps: duplication of the ROI (Fig. 3A.); application of a 10-pixel Gaussian filter so that fine and medium structures were eliminated and only large variations in density remained (Fig. 3B.); subtraction the second image from the first (Fig. 3C.); transformation of the resulting image into a binary 8-bit image (Fig. 3D.); skeletonization and outlining the bone trabeculae (Fig. 3E.), resulting in the bone trabeculae being clearly outlined. This figure also discloses the graph of FD analysis (Fig. 3F). In total, two FD measures were obtained, one for each ROI.





size	count
2	99
3	63
4	47
6	24
8	15
12	8
16	4
32	1
64	1

Figure 3. Image processing method for fractal dimension analysis. A. Duplication. B. Gaussian filter at 10.00 pixels. C. Subtraction of the second image from the first. D. Turning image into a binary 8-bit image, E. Skeletonization and outlining the bone trabeculae. F. The box counting procedure and calculation is also represented by a graph.

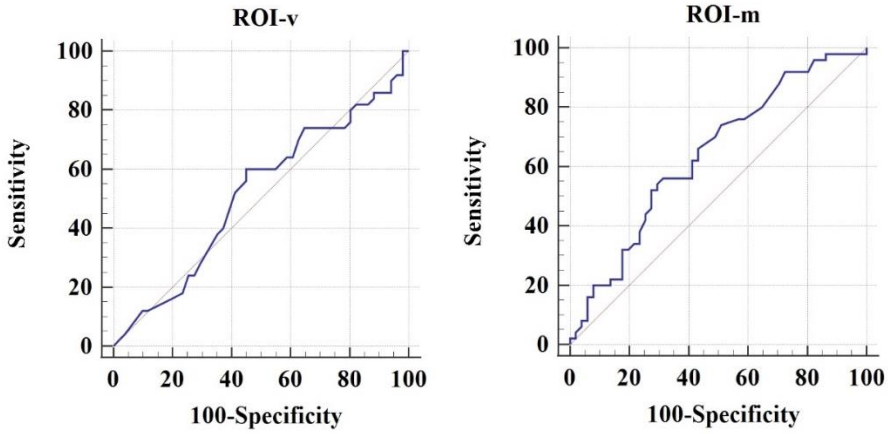


Figure 4. Receiver operating characteristic (ROC) curves of the fractal dimension analysis at the vertebral (A) and mandibular (B) sites.

The images were analyzed on a high-resolution LCD computer monitor (1280 x 1024) in a dark environment. For intraobserver reliability, one observer analyzed the FD twice within a one-week interval. For interobserver reliability, the results of the analysis of two independent observers were compared. The two observers were oral and maxillofacial radiologists with over four years of experience with CBCT exams. Neither observer was aware of the DXA results.

3.2.3 **STATISTICAL ANALYSES**

After checking the normal distribution of the FD analysis results, age, height and weight data, and homoscedasticity (Shapiro-Wilk test and Cochran test), the analyses were performed. To test the hypothesis of equality of mean FD on each ROI, age, height and weight between the groups (women with normal BMD and osteoporosis), the Student's t test was applied to the variables that agreed with the assumptions of normality and homoscedasticity, and the non-parametric Mann-Whitney test for the variables that were not in accordance with such assumptions. The correlations between the measurements were verified by correlation coefficients.

The receiver operating characteristic (ROC) curve analysis was used to analyze the accuracy of FD measurements on each ROI. The area under the ROC curve (AUC) defined the accuracy of the methods, as previously proposed.[33] The accuracy of FD measurements in the diagnosis of osteoporosis was calculated for the optimal thresholds.

Regarding intra- and interobserver agreements, the calculated values of FD were compared, following the Bland & Altman method,[34] which results in a 'coefficient of repeatability' for repeated measurements that is twice the standard deviation of the differences between them. According to the method, the precision of the measurements was classified as: excellent (<10%), good to moderate (10 to 20%), low (>20%).

A P value less than 0.05 was considered statistically significant for all tests. The statistical analyses were performed by Statistica 7.0 software (ver. 7, Stat Soft, Inc, 2004, Statistica, Tulsa, OK, USA) and Medcalc 16.8.4 (Medcalc Software bvba, Ostend, Belgium).

3.2.4 **RESULTS**

The comparison of descriptive data between postmenopausal women with normal BMD and osteoporosis is demonstrated in Table 1. The mean values for height, weight, BMDs at the three bone sites, and FD at the mandibular site (ROI-m) were significantly lower in the osteoporotic group compared to postmenopausal women with normal BMD. The mean values of FD did not present statistically significant differences at the vertebral site between both studied groups.

Table 1. Comparison of mean values of descriptive data between postmenopausal women with normal bone mineral density and osteoporosis

Variables	Normal BMD	Osteoporosis
BMD L1-L4 (g/cm^2)	1.202 ± 0.131	0.797 ± 0.064**
BMD FN (g/cm^2)	1.022 ± 0.116	0.765 ± 0.101*
BMD TH (g/cm^2)	1.075 ± 0.109	0.789 ± 0.125*
FD ROI-v	1.80 ± 0.17	1.80 ± 0.18
FD ROI-m	1.76 ± 0.23	1.65 ± 0.26**
Age (years)	64.85 ± 9.78	63.94 ± 9.95
Height (cm)	157.73 ± 7.32	151.73 ± 6.34**
Weigth (kg)	73.21 ± 10.85	59.07 ± 10.71*

BMD: bone mineral density, FN: femoral neck, TH: total hip, L1: first lumbar vertebra, L4: fourth cervical vertebra, FD: fractal dimension, ROI-v: region of interest in the second vertebra, ROI-m: region of interest in the panoramic reconstruction image of the mandible, *: $p<0.05$ by t test), **: $p<0.05$ by Mann Whitney test.

Regarding intraobserver agreement, most of the measurements were between the limits of agreement (±2SD). The mean difference between the measurements were -0.02 [-0.19, 0.16; 95% limits of agreement] for the ROI-v and -0.07 [-0.63, 0.49; 95% limits of agreement] for the ROI-m. The precision for ROI-v was 9% and the precision for ROI-m was 35%.

Regarding interobserver agreement, most of the measurements were also between the limits of agreement (±2SD) with mean differences between the measurements of 0.2 [-0.45, 0.86] for the ROI-v and of -0.31 [-1.05, 0.41] for the ROI-m. A lower precision was found for both ROIs compared to intraobserver values (44% for ROI-v and 55% for ROI-m).

There was no correlation between the FD analyses (ROI-v and ROI-m) and the age, weight and height of patients ($p>0.05$). FD analyses at the vertebral and mandibular sites, following the proposed method, resulted in no correlation with BMDs at the lumbar spine, FN and TH, as shown in Table 2.

Table 2. Correlation coefficients between fractal dimension measurements and bone mineral density at the lumbar spine, femoral neck and total hip

	BMD L1-L4	BMD FN	BMD TH
ROI-v	-0.075*	-0.145*	-0.103*
ROI-m	0.059*	0.058*	0.059*

ROI-v: fractal dimension at the region of interest in the vertebral site, ROI-m: fractal dimension at the region of interest in the mandibular site, L1: first lumbar vertebra, L4: fourth lumbar vertebra, FN: femoral neck, TH: total hip, BMD: bone mineral density *p>0.05 (not statistically significant).

The AUC was 0.531 (p=0.720) at ROI-v, and for ROI-m the AUC was 0.644 (p=0.008). ROC curves for the ROI-v and ROI-m are represented in Figures 4A and B, respectively. For a FD of 1.703 at the mandibular ROI (the cutoff threshold), the following accuracy measurements were verified: sensitivity of 54.9%, specificity of 71.1%, positive predictive value of 65.1%, and a negative predictive value of 61.7%.

3.2.5 DISCUSSION

This study compared FD analysis of the vertebral and the mandibular trabecular bone between postmenopausal women with osteoporosis and normal BMD according to DXA at the lumbar spine and proximal femur. The FD analysis of the mandibular bone presented lower mean values in osteoporotic women than in women with normal BMD. On the other hand, the vertebral measurements did not differ significantly between women with normal BMD and osteoporosis.

To the author's knowledge, this is a pioneer diagnostic test study that evaluated the accuracy of FD measurements on CBCT to identify postmenopausal women with osteoporosis. Amongst two different measurements (ROI-v and ROI-m), only the FD

of the mandible (ROI-m) demonstrated accuracy to identify postmenopausal women with osteoporosis. Nevertheless, the accuracy of this measurement was low, of which the area under the curve was 0.644. At a FD value of 1.7 in ROI-m, the sensitivity of FD to identify postmenopausal women with osteoporosis was 54.9% with a specificity of 71.1%. In a previous study with dental panoramic radiographs, some authors found an AUC of 0.78 for mandibular FD to identify women with osteopenia (T-Score ≤ -1.0). With a similar cut point of 1.7 for FD, the sensitivity was 84.6% with a specificity of 40%.[16] However, it is not possible to compare both results directly. Although FD was analyzed at the mandibular trabecular bone on both studies, different imaging modalities preclude the direct comparison. Moreover, in the present study the outcome was related to osteoporotic women, whereas in the previous study the measurements were related to osteopenia.

Some previous studies have found differences in FD values between individuals with osteoporosis and with normal BMD.[17,18] Controversially, FD was similar to both groups in other studies.[14,15,35] The divergent results may be due to different methodological approaches, including image processing for FD calculation. In the present study, a Gaussian filter at 10 pixels was used. In most previous studies with intraoral and panoramic radiographs, Gaussian filter at 35 pixels was applied to get rid of brightness variations due to overlapping soft tissue and variable bone thickness.[14-19,35] These controversial studies were based on radiographs. Therefore, these studies had a great limitation due to the two-dimensional representation of the images and great structure overlap. On the other hand, in the present study a low-pass filtering was considered to be tested, based on a previous CBCT study.[32]

To our knowledge, only two studies have compared FD analyses of the jawbones on CBCT scans with BMD according to DXA.[26,27] The former study compared

FD analysis between 25 women with normal BMD and 25 women with osteoporosis according to DXA only at the lumbar spine.[26] A circular region of interest of 20 x 20 pixels was selected on coronal images below the roots of the premolar and the mental foramen. A negative correlation was found between FD and lumbar spine BMD. Although control group showed lower FD values than the osteoporotic group, no significant difference was found between the two groups. In our study, FD values at the mandibular trabecular bone was significantly lower in the osteoporotic group and no correlation was found between mandibular FD values and BMD at the lumbar spine, FN, and TH.

In the other aforementioned observational study that compared FD at the jawbones with BMD, FD measurements were performed in different locations, one in the condyle, other in the maxilla and the last in the inferior cortex of the mandible.[27] The ROI sizes were 40x30, 14x14, and 12x12-pixel areas, respectively. FD measurements were compared amongst 26 patients who had osteoporosis according to DXA at the lumbar spine and hip, 33 who had osteopenia and 31 with a normal BMD. Only the ROI located on the left side of the maxilla showed significant lower results in osteoporotic individuals than in the control group. The image processing method for FD analysis did not follow any traditional parameters, like the ones used by White & Rudolph in 1999.[31]

In agreement with other authors, it is possible that the discrepancies of results in all previous researches using FD measurements on dental imaging modalities could likely be explained by anatomical variations, different methods used to obtain 2-dimensional or 3-dimensional bone images and differences in selecting the areas to be measured or in the methods applied to obtain FD results.[36]

A recent research evaluated the reliability of FD measurements on CBCT scans. However, the authors compared results obtained in patients with medication-related osteonecrosis of the jaw using different ROIs. It showed a good reproducibility regarding to FD assesments.[37] The selection of ROI-v, in this study, at the cervical vertebra was based in a recent study with 38 postmenopausal women, the authors verified that radiographic density analysis of the second cervical vertebra showed significant correlation with lumbar and femoral BMDs.[29] The authors concluded that this ROI has a great potential to detect bone changes caused by osteoporosis. On the other hand, the authors recognized that the measurement was very subjective and susceptible to variations in different exposure parameters, possibly presenting different results from two exams of the same patient using the same tomography device.[29] Some authors have demonstrated that bone structure patterns, including FD, are not affected by the exposure time. On the other hand, these bone parameters are heavily affected by the voxel size.[38]

A recent systematic review and meta-analysis showed that, to date, FD measures on dental radiographs have not been able to distinguish individuals with osteoporosis from healthy control group significantly.[39] The scarcity of CBCT studies and the need for further standardized studies, especially concerning FD calculation (regions for FD assessment; images processing technique; methods for FD measurement) were observed. This result is in line with the present study in which FD analysis at the vertebral site could not be used as a complementary tool to refer postmenopausal women for further densitometric investigation. The box counting method was chosen to evaluate FD at two distinct bone sites, using two different image-processing methods. However, as all the previous studies that tested the correlation between FD and skeletal BMD,[26,27] the selected ROI was bi-dimensional.

Therefore, despite using a three-dimensional imaging modality, the bone texture parameter (FD) is being measured two-dimensionally on multiplanar reconstruction images similarly to conventional radiographs, with the exception of soft tissue overlap. Future studies should be performed by using software in which microstructural bone parameters could be measured three-dimensionally. Image processing protocol should also be standardized for CBCT studies using FD.

The present study has other limitations, including the use of a convenience sample based on a DXA database. The correlation between FD and BMD was tested, which can be considered a promising bone texture image parameter more related to bone quality and a parameter related to bone strength, respectively. Therefore, the association of FD or other bone texture parameters on CBCT should also be considered in further research, as well as the inclusion of osteopenia patients.

In conclusion, based on our image processing protocol for FD analysis, lower values of FD on the mandibular trabecular bone were found in osteoporotic women in comparison to women with normal BMD. Nevertheless, no differences were found for the vertebral measurements. Furthermore, none of the measurements produced highly accurate and reliable results for detecting postmenopausal women with low BMD.

Conflicts of Interest: None

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4. CAPÍTULO 4 – ARTIGO EM DESENVOLVIMENTO

4.1 ARTIGO C:

Mandibular cortical width on TCFC may predict hip fracture risk

Artigo em desenvolvimento para submissão na Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 2022

4.1.1 ABSTRACT

Objective: To assess the relationship between mandibular cortical width measured on Cone-Beam Computed Tomography (CBCT) of postmenopausal women and fragility fractures risk evaluated by FRAX.

Study design: The sample consisted of 46 postmenopausal women that had previously underwent dual-energy x-ray absorptiometry (DXA) and cone-beam computed tomography (CBCT) exams. Fracture Risk Assessment Tool was applied. Hip and major osteoporotic fracture risks in ten years were calculated by FRAX and the cut-offs of 3% and 15% were considered for both fracture types, respectively. Mandibular cortical width (MCW) was measured on CBCT scans.

Results: Hip fracture risk was associated with BMD results. MCW correlated with both BMD at all skeletal sites ($p<0.001$). Moreover, Regarding fracture risk, MCW values presented significant negative correlations with both FRAX results ($r = =0.607$ for hip fracture risk and $r = -0.543$ for major osteoporotic fracture risk). The area under the curve of MCW was 0.903 to identify a high hip fracture risk.

Conclusion: Correlations were found between MCW, DXA and FRAX results. MCW on CBCT scans can be potentially be used as fracture risk predictor, especially trabecular number at the mandibular site.

Key Words: Osteoporosis; Cone-Beam Computed Tomography; Trabecular Bone Microarchitecture; FRAX.

4.1.2 INTRODUCTION

Osteoporosis is a skeletal disease characterized by decreased bone strength. Bone strength is given by the integration between bone mineral density (BMD) and bone quality.[1] In the presence of osteoporosis, bone fragility is increased and, consequently, the predisposition of affected individuals to fragility fractures, where bones can break from low level impact or stress that would not normally break a healthy bone.[2].The disease mainly occurs in postmenopausal women and elderly men.[3]

With a worldwide ageing population, the importance of the prevention and management of osteoporotic fragility fractures is increasing over time.[4] Fractures at the hip and vertebrae are among the most common and serious sites of osteoporotic fracture. Fragility fractures of the humerus, forearm, ribs, tibia, pelvis and other femoral fractures after the age of 50 years are also fractures associated with low BMD.[5]

Osteoporotic fractures decrease the quality of life of affected individuals, increase the number of hospital admissions, and may lead to increased mortality. Considering its socioeconomic burden, early identification of high-risk individuals and prevention of fragility fractures have become a public health priority.[2,5,6]

However, early identification is challenging. Diagnosis is usually made by BMD assessment using dual-energy X-ray absorptiometry (DXA). Low BMD combined with other risk factors is mandatory for osteoporosis treatment and fracture risk reduction.[7-9] Although DXA is considered the gold standard for disease diagnosis, its high cost and lower availability prevent its use for osteoporosis screening Moreover, many individuals with normal BMD at DXA present osteoporotic fractures possibly associated to bone microarchitecture.[10-12]

Therefore, methods to identify high-risk fracture individuals and low BMD are crucial. Fracture Risk Assessment Tool (FRAX) has been widely used in clinical practice to calculate hip and major osteoporotic fracture risk in 10 years.[13-18] This

algorithm has been validated However, it has its own limitations and the evaluation may be more precise if added to additional methods, such as image analysis.[18]

Cone-Beam Computed Tomography (CBCT) exam is widely used in the elderly population, especially for implant planning, and mandibular changes have already been reported in patients with osteoporosis on CBCT scans.[19-23] However, these previous studies compared CBCT findings with DXA results. Accordingly, it is necessary to verify whether this exam could serve as an auxiliary tool for identifying the highest fracture risk group. This study aimed at verifying the relationship between MCW measurement and FRAX results. Furthermore, the accuracy of MCW to predict higher fracture risk was also analyzed.

4.2 Patients and methods

4.2.1 Patients selection

Postmenopausal women that had underwent DXA and CBCT scans from a previous study (103 patients) were called for FRAX application. However, only 46 responded. In this study, 100 postmenopausal women that had previously underwent DXA and CBCT exams were initially selected. All these patients were called for application of FRAX tool, but only 46 responded. Patients with any osteometabolic disease except osteoporosis, or using medications associated with reduced bone mass or with the presence of a disease causing secondary osteoporosis were excluded from the study. This study was approved by the Ethics Committee in Research and in accordance with the 1964 Helsinki declaration. All patients signed an informed consent.

4.2.2 BMD assessment

Lunar DPX NT device was used for DXA exams (GE Healthcare, Madison, Wi, USA) acquired by a single operator. BMD assessment followed the World Health Organization (WHO) criteria: normal BMD (T-Score ≥ -1.0); osteopenia (T-score between -1.0 and -2,5), osteoporosis (T-Score ≤ -2.5). Patients with osteopenia were not included to avoid midterm results.

4.2.3 CBCT measurement

CBCT scans were acquired on I-CAT Classic device (Imaging Sciences International, Inc., PA, USA) at the University Hospital of Brasília, by the same operator. The following image parameters were selected: 120kVP, 8mA, field of view (FOV) of 20 x 8 cm and 0.25mm of voxel size. These images were evaluated on Xoran 3.1.62 (Xoran Technologies, Ann Arbor, Mi, USA). They were also converted to DICOM format using the same program.

Panoramic reconstructions and transaxial sections were performed on each CBCT scan. To obtain these sections, Figure 1 demonstrates the standardization for measuring MCW:

- On the multiplanar reconstruction (MPR) screen, the mandibular base was aligned on the coronal section (Figure 1A). A "sharpen low 3x3" filter was applied to the images for evaluation.
- In the same previous screen, but now in the axial section, the mandibular ramus was aligned to the cursor (Figure 2B).

- The thickness of the sagittal slice on this screen was adjusted to 75.00 mm for better alignment of the inferior-most point of the mandibular symphysis with the most inferior point of the mandibular angle (Figure 7C).
- On the axial section, at the height of the middle third of the roots of the teeth, when present, a parabola was drawn in the center of the mandibular alveolar ridge (Figure 7D). From this parabola traced with the computer cursor the transaxial sections were obtained and mandibular cortical width was measured (Figures 7E, 7F and 7G).

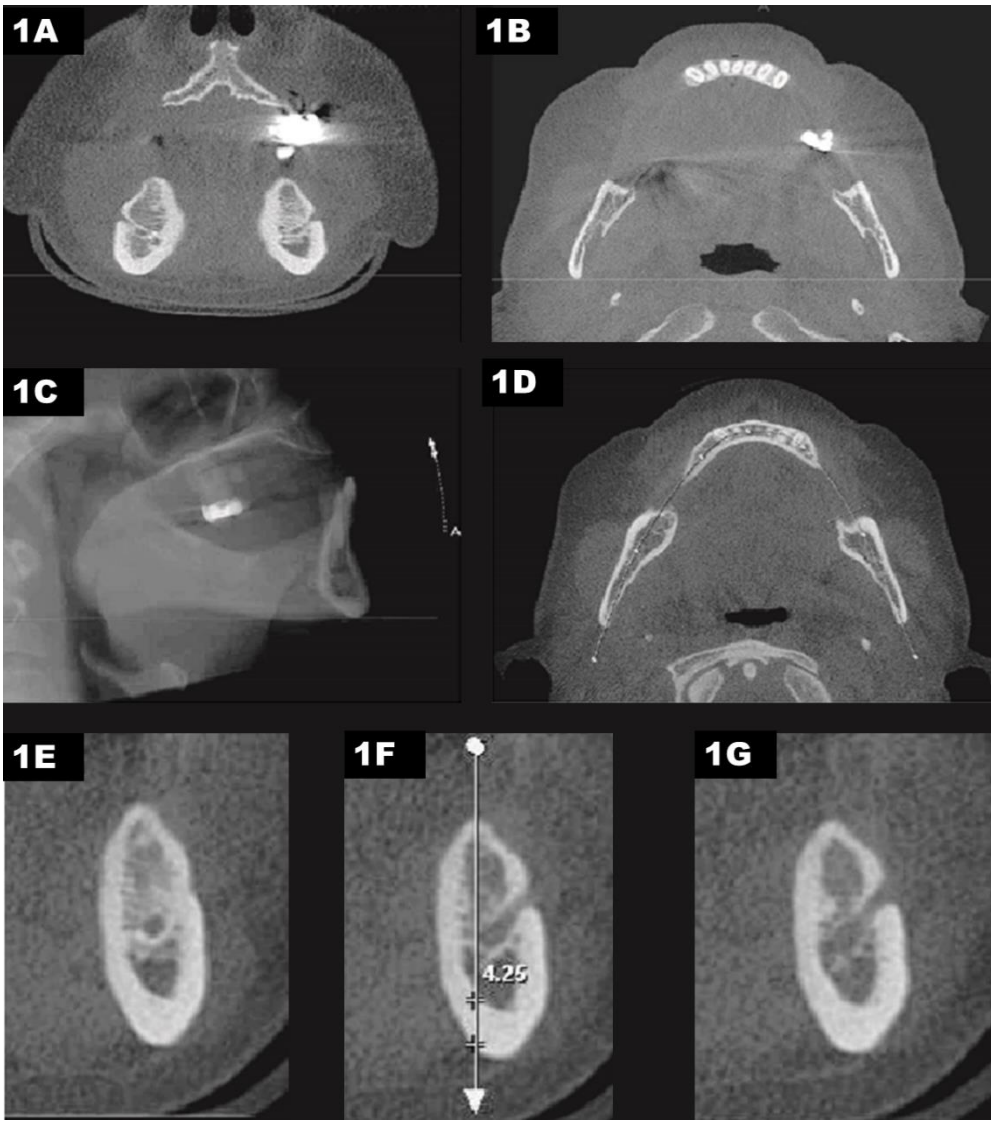

Figure 1 – Standardization on CBCT sections to measure MCW.

4.2.4 FRAX evaluation

FRAX tool was applied to the studied patients. The FRAX questionnaire was accessed in the website page for the Brazilian population (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=55). In such tool, seven dichotomous clinical risk factors were analyzed during patient interview: prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, rheumatoid arthritis, and other causes of secondary osteoporosis. In addition to age and sex and body mass index (BMI), these risk factors contribute to estimating a 10-year fracture probability, independent of bone mineral density (BMD). Although BMD at the femoral neck is an optional input variable, we have used such information as all the patients had performed DXA at this bone site.

The Brazilian FRAX Para avaliação do risco de fratura, considerou-se o ponto de corte proposto no FRAX brasileiro de 3% para o risco de fratura de quadril. Ou seja, foram consideradas mulheres com alto risco de fratura de quadril as que apresentassem um valor igual ou maior que 3% em 10 anos, pela ferramenta FRAX.

4.3 Statistical analysis

In addition to the descriptive analysis, correlations between quantitative variables were verified using Spearman's correlation test. The association between qualitative variables was analyzed using the chi-square test. Differences in the values of cortical and trabecular CBCT measurements between the two fracture risk groups (<3% and ≥3%) were analyzed using the non-parametric Mann-Whitney test. A linear logistic regression model evaluated the estimates of the effect of mandibular inferior cortical thickness values on fracture risk. In addition, the accuracy of the measurement

of mandibular cortical thickness to predict increased risk of hip fracture was analyzed by calculating measures of sensitivity, specificity, area under the ROC curve and likelihood ratios.

Statistical analyses were performed using Statistica 7.0 (StatSoft, Inc, 2004, Statistica, version 7, Tulsa, OK, USA, www.statsoft.com) and Medcalc 16.8.4 (Medcalc Software bvba, Ostend, Belgium, https://medcalc.org, 2016) software. A p value < 0.05 was considered statistically significant for all statistical tests.

4.4 RESULTS

The mean age of the 46 women was 63.2 (± 9.5 years). From the total sample, 24 women presented osteoporosis and 22 had normal BMD (Table 1). Thirteen of them (28.3%) presented a 10-year risk of developing a hip fracture equal or higher than 3%. Only four women presented a major osteoporotic fracture risk in 10 years equal or higher than 15%. There was association between the densitometric diagnosis (DXA) and hip fracture risk evaluated by FRAX (Chi-square, p<0.05).

Table 1 – Distribution of the 46 postmenopausal women according to DXA and FRAX results, considering the cut-off values

DXA result	**Hip fracture risk**		**Major osteoporotic fracture risk**	
	Low risk (<3%) N	High (≥3%) N	Low (<15%) N	High (≥15%) N
Normal BMD	22	0	21	1
Osteoporosis	11	13	21	3
p-value	0.0001*		0.138	

Table 2 discloses the descriptive statistics of the mandibular cortical width and BMD values according to FRAX thresholds. BMD and MCW mean values were significantly different between individuals with higher hip fracture risk (≥ 3%) and lower fracture risk (< 3%).

There were positive correlations between MCW measurements and BMD at the lumbar spine (r =0.473), total hip (r = 0.479) and femoral neck (r = 0.478). Regarding fracture risk, MCW values presented significant negative correlations with both FRAX results (r = =0.607 for hip fracture risk and r = -0.543 for major osteoporotic fracture risk). Table 3 presents the results of the linear regression models, estimating the effect of MCW values on both FRAX results.

Table 2 – Descriptive statistics of BMD at the three bone sites (lumbar spine, femoral neck and total hip) and mandibular cortical width according to FRAX thresholds.

FRAX (hip fracture risk)	Mean	Median	LL	UL	p-value*
BMD L1-L4 (g/cm^2)					
<3%	1.06	1.09	0.65	1.49	<0.001
>=3%	0.78	0.77	0.71	0.88	
BMD femoral neck (g/cm^2)					
<3%	0.94	0.93	0.69	1.26	<0.001
>=3%	0.69	0.70	0.60	0.76	
BMD total hip (g/cm^2)					
<3%	0.98	1.00	0.64	1.39	<0.001
>=3%	0.73	0.72	0.59	0.89	
Mandibular cortical width (mm)					
<3%	2.96	3.00	1.25	4.50	0.002
>=3%	2.06	2.13	1.00	3.50	

FRAX = Fracture Risk Assessment Tool; LL = lower limit, UL = upper limit; BMD L1-L4 = bone mineral density at the lumbar spine

Table 3 – Estimation of the effect of MCW on fracture risk (FRAX evaluation). Estimativas do efeito dos valores da espessura da cortical inferior da mandíbula no risco de fratura.

Responding variable (y)	Beta	95% Confidence Interval	
		LL	UL
Major osteoporotic fracture	-2.38	-3.85	-0.90
Hip fracture	-1.61	-2.47	-0.75

A high accuracy of MCW to predict a high risk of hip fracture (above 3%) in 10 years was yielded, with an area under the ROC curve of 0.903 (Figure 2)

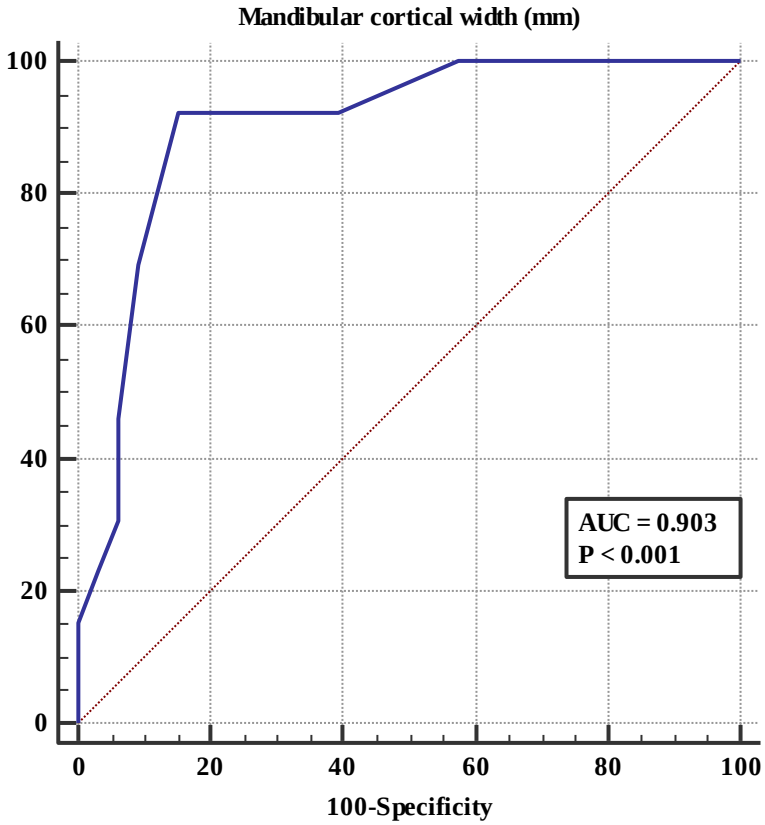

Figure 2 – ROC curve of MCW measurement to predict hip fracture risk based on FRAX threshold of 3%.

Based on the ROC curve (Youden index), a cut-off point of 2.25mm was achieved for MCW measurement. Table 4 discloses the sensitivity, specificity and likelihood ratios of this cut-off value to predict a higher hip fracture risk.

Table 4 – Accuracy measurements of MCW (cut-off point of 2.25mm) to predict a higher risk of hip fracture risk, considering FRAX threshold of 3%.

Accuracy measurements (95% CI)	
Sensitivity	92.31 (64.0 – 99.8)
Specificity	84.85 (68,1 – 94.9)
Likelihood ratio +	6.09 (2.7 – 13.9)
Likelihood ratio -	0.091 (0.01 – 0.6)

4.5 PRELIMINARY DISCUSSION

To the best of the author's knowledge, this is the first study to verify a potential use of the mandibular cortical index, which analyzes MCW close to the mental foramina, to predict FRAX results. A positive correlation was found between cortical thickness and BMD at the lumbar spine and hip. Moreover, MCW values correlated negatively with higher risk of hip and major osteoporotic fractures. In other words, the lower the cortical thickness, higher is the 10-year fracture probability on FRAX. Based on an intervention threshold of 3% for the risk of hip fracture in the Brazilian FRAX, it was also found that a cortical thickness of 2.25 mm was able to accurately predict individuals at increased risk for this type of fragility fracture. As the proportion of individuals living to older age is increasing rapidly worldwide, MCE seems to be potentially used to screen high-risk individuals that undergo to dental treatment and CBCT examination.

Several studies have evaluated cortical and trabecular bony changes to identify individuals with low BMD on conventional radiographs.[25-41] Nonetheless there is scarcity of CBCT studies for the same purpose. The few CBCT studies were usually variations and modifications of the indices applied to panoramic radiographs.[19-23, 42-44]

In the present study, there was an association between the increased risk of fracture and the presence of osteoporosis, a result that was already expected due to the drop in BMD directly influencing bone strength. However, the correlation with FRAX data is the key point for future studies that may evaluate the potential of bone microarchitecture assessment associated with cortical analysis for bone quality analysis.

A previous longitudinal study demonstrated that that FRAX value >15% together with larger trabecular spacing are good predictors of major fracture due to

osteoporosis. The authors stated that the results are similar to FRAX using the BMD result given by DXA.[45]

The results showed significant differences in the cut-off points of MCW assessed on a previous study using CBCT cross-sections to identify women with and without osteoporosis.[23] A thickness of 2.75 mm was described as a cut-off point for this purpose while the cut-off point for fracture risk was 2.25 mm in the present study.

Another longitudinal study with 10-year follow-up analyzed mandibular cortical bone of men and women on panoramic radiographs. The results of this study revealed significant relative fracture risk in patients with FRAX above 15% and mandibular cortical bone with a severely eroded appearance. However, there was no strong correlation between mandibular cortical thickness <3mm and the risk of bone fracture. On the other hand, a recent study with panoramic radiographs also found strong correlations between lower MCW values and FRAX results.[46]

The present study considered an intervention threshold of 3% proposed by FRAX Brazil. MCW values were significantly lower in patients at increased risk of fracture when compared to patients without risk of fracture. In the present study, the quality of the mandibular cortical bone was not taken into account. However, a previous study from our group demonstrated strong correlation between mandibular cortical erosion and DXA diagnosis.[23]

Notwithstanding the small sample size, this study indicated that mandibular cortical thickness may serve as an auxiliary tool in the screening of individuals at increased risk of fracture by FRAX. Future perspectives involve the automatic identification of these patients with artificial intelligence tools, which will also allow the integration of image characteristics with the patient's clinical risk factors.

To sum up, MCW values were significantly lower in women with higher fracture risk and there was a correlation between this measurement and the FRAX results. Considering the FRAX intervention threshold of 3% of 10-year probability of hip fracture, MCW below 2.25mm may identify high-risk individuals for presenting such skeletal fracture. Further studies should be performed in male and also with other populations, considering the variety of country-specific intervention thresholds to demarcate high-risk patients.

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5. DISCUSSÃO GERAL

5.1 DISCUSSÃO GERAL E CONCLUSÕES FINAIS

5.2 Discussão geral

A tese analisou diferentes parâmetros ósseos corticais e trabeculares em TCFC de mulheres na pós-menopausa e suas relações com o diagnóstico densitométrico de osteoporose e o risco de fratura avaliado pela ferramenta FRAX. A TCFC demonstrou acurácia para predizer o resultado do exame de DXA, com o desenvolvimento de um novo índice qualitativo e quantitativo denominado 3D MOI, conforme apresentado no artigo A (de Castro et al. 2020). Por outro lado, a análise da dimensão fractal não demonstrou boa acurácia e reprodutibilidade para predizer a osteoporose, conforme evidenciado no artigo B (Carvalho et al. 2022) e no artigo C.

O artigo A foi o primeiro estudo de teste diagnóstico que analisou a acurácia e reprodutibilidade dos índices qualitativos e quantitativos em TCFC para identificar pacientes com baixa DMO, e apresenta um modelo preditivo para identificar pacientes osteoporóticos com base na idade do paciente e nas medidas de TCFC, com a criação de um índice tridimensional denominado 3D MOI. Diferenças significativas entre mulheres na pós-menopausa com DMO normal e mulheres na pós-menopausa com osteoporose foram encontradas nos valores de espessura da cortical medidos na reconstrução panorâmica e nos cortes transaxiais. Estas medidas também apresentaram uma correlação positiva com as DMO da coluna lombar, do colo do fêmur e do quadril total. Além disso, foi encontrada uma associação entre a análise visual da qualidade da cortical mandibular e a DMO. O modelo preditivo que combina as três medidas da TCFC com a idade demonstrou a maior área sob a curva ROC (0,8). Assim, este modelo pode ser eficaz como uma ferramenta adjuvante para identificar mulheres na pós-menopausa com baixa DMO que foram submetidas a

exames de TCFC para fins odontológicos. Apenas um estudo prévio recente havia analisado a acurácia do índice qualitativo muito usado em radiografias panorâmicas que classifica a cortical em C1, C2 e C3 (Kato et al. 2019). Para esta avaliação, os autores encontraram valores de acurácia inferiores aos encontrados no presente estudo, com área sob a curva ROC de 0,576 94 e fizeram as avaliações em reconstruções panorâmicas com diferentes espessuras. No artigo A, houve um aperfeiçoamento da metodologia utilizada, sendo que o novo índice apresentado se baseou em análise qualitativa e quantitativa da cortical em reconstruções panorâmicas e transaxiais. Além disso, o modelo preditivo levou em consideração também o fator de risco idade e a somatória do índice com este fator apresentou uma alta acurácia para predizer o diagnóstico de osteoporose. Portanto, o 3D MOI pode ser eficaz como uma ferramenta adjuvante para identificar mulheres na pós-menopausa com baixa DMO que foram submetidas a exames de TCFC para fins odontológicos. Resta ainda aplicar este modelo em outras populações além das mulheres na pós menopausa.

O artigo B (Carvalho et al. 2022) fez a avaliação do trabeculado ósseo por dimensão fractal na TCFC, utilizando a mesma amostra de mulheres na pós-menopausa do artigo A (de Castro et al. 2020). Os valores médios de dimensão fractal foram significativamente menores na região mandibular de interesse (ROI-m) das pacientes com osteoporose quando comparados às pacientes com DMO normal. No entanto, as áreas sob a curva ROC foram 0,644 (p=0,008) e 0,531 (p=0,720) para os locais mandibulares e vertebrais.

Apenas dois estudos, Mostafa et. al (2016) e Güngor et al (2016), compararam as análises de dimensão fractal na mandíbula com dados do exame de DXA, sendo que estes estudos apresentaram resultados controversos. Mostafa et al. (2016) utilizaram uma amostra mais reduzida de mulheres (25 com osteoporose e 25 com DMO normal)

e correlacionaram os dados apenas com DXA da coluna lombar. Güngör et al (2016) também avaliaram a dimensão fractal, porém em sítios distintos aos dos demais estudos (na cabeça da mandíbula, na maxila e na cortical mandibular). Somente a região de interesse localizada no lado esquerdo da maxila mostrou resultados significativamente menores em indivíduos osteoporóticos do que no grupo de controle.

O artigo B demonstrou que, apesar de diferenças na dimensão fractal mandibular entre pacientes com osteoporose e com DMO normal, esta análise não apresentou boa acurácia e reprodutibilidade para predizer o diagnóstico densitométrico. Uma limitação do artigo B foi o fato da análise ter sido feita após a seleção de uma região de interesse (ROI) em um corte. Ou seja, foi feita uma análise bidimensional em um exame tridimensional.

A escolha da ferramenta para análise do risco de fratura no artigo C foi baseada em sua ampla aplicabilidade no mundo e sua validação nos diversos países, incluindo o Brasil (Borgström et al. 2020, Aspray et al 2015). A ferramenta FRAX é de simples aplicação e pode ser feita por qualquer profissional de saúde treinado, incluindo o cirurgião-dentista. Apesar de resultados aparentemente desfavoráveis com a análise da DF, a observação da cortical óssea mandibular se faz válida como ferramenta para predizer baixa densidade mineral óssea e risco de fratura (Carvalho et al. 2022). A avaliação da TCFC pelo radiologista e o laudo deste exame precisa incorporar a análise da cortical mandibular, para que o paciente de alto risco possa ser identificado. Essa seria uma estratégia de avaliação “oportunista” de osteoporose no paciente que necessita realizar o exame de imagem odontológico, por exemplo para planejamento de implantes.

O artigo C apresenta a medida da espessura da cortical mandibular como indicativo de risco à fratura. O artigo A (de Castro et al. 2020) apresentou como ponto

de corte a cortical mandibular menor que 2,75mm para predizer baixa DMO de coluna e de fêmur, cabendo ao cirurgião-dentista encaminhar os pacientes para a realização do exame densitométrico para diagnóstico da osteoporose. Já o artigo C relacionou o ponto de corte menor ou igual a 2,25mm com o risco a fratura segundo o FRAX Brasil. Fica claro que a diminuição da espessura da cortical mandibular pode representar DMO compatível com o diagnóstico de osteoporose e agora também predizer o risco à fratura de quadril.

O cirurgião dentista deve fazer parte de uma ação global, envolvendo os demais profissionais de saúde, associações de pacientes e os responsáveis pela formulação de políticas públicas para que a população receba mensagens claras, consistentes e persuasivas em relação à saúde óssea. Também há uma necessidade urgente de comunicações baseadas em evidência que destaquem os riscos que a osteoporose não tratada oferece à qualidade e ao tempo de vida das pessoas que têm a doença. O perfil do cirurgião-dentista precisa mudar, não apenas desenvolvendo habilidades e competências na área de comunicação, mas também na área técnica, pois, o conhecimento das doenças crônicas mais prevalentes no Brasil, como hipertensão, diabetes e osteoporose, deverá fazer parte da rotina de diagnóstico do cirurgião-dentista. Possivelmente, caberá aos profissionais da odontologia o papel de monitoramento dessas afecções (Pyle, 2012), considerando a mudança do padrão epidemiológico devido ao envelhecimento populacional.

Assim, sempre que uma tomografia computadorizada for realizada para indicações clínicas específicas, como implantes dentários, um índice como o 3D MOI pode ser realizado para avaliar qualitativa e quantitativamente a condição da cortical mandibular. Isso certamente pode ser útil para avaliar o status da

osteoporose na população idosa e, mais especificamente, em mulheres na peri ou pós-menopausa.

Cabe destacar que o acesso aos serviços odontológicos é mais simples e menos oneroso ao paciente. Isso significa que, de forma oportunística, ao realizar um exame por imagem, o cirurgião-dentista tem a oportunidade de suspeitar, ou até mesmo identificar doenças crônicas. Tem-se hoje a Revolução 4.0. da biotecnologia, da radiômica, e a presença de inteligência artificial, e, portanto, pode-se esperar que essa revolução tecnológica impactará na forma de atenção à saúde. Logo precisaremos que este novo índice 3D MOI seja aplicado, não de forma manual pelo radiologista, mas de maneira automatizada. Esse é papel que a sociedade espera da ciência.

5.3 Conclusões finais

O presente estudo demonstrou que parâmetros ósseos corticais mandibulares qualitativos e quantitativos analisados em TCFC foram capazes de predizer o diagnóstico densitométrico de osteoporose.

Um modelo preditivo de identificação da doença foi desenvolvido com acurácia de 0.8 (área abaixo da curva ROC), com a somatória de medidas qualitativas e quantitativas da cortical mandibular em TCFC com o fator de risco idade. Nesse sentido, mulheres idosas com espessura da cortical abaixo de 2,75mm e com cortical classificada em C3 precisam ser encaminhadas para investigação da osteoporose.

Mulheres na pós-menopausa apresentaram valores de dimensão fractal significativamente menores em relação às mulheres com DMO normal nos exames de TCFC, porém a análise deste parâmetro ósseo trabecular na mandíbula e na vértebra

C2 não apresentou acurácia e boa reprodutibilidade para predizer o diagnóstico densitométrico de osteoporose.

A espessura da cortical mandibular igual ou menor a 2,25mm em mulheres na pós-menopausa pode ajudar a predizer risco de fratura de quadril em 10 anos.

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6. ANEXO

6.1 Anexo 1

DETALHAR PROJETO DE PESQUISA

DADOS DA VERSÃO DO PROJETO DE PESQUISA

Título da Pesquisa: Espessura e qualidade da cortical óssea mandibular avaliada por tomografia computadorizada de feixe cônico em mulheres na pós-menopausa e homens acima de 60 anos.
Pesquisador Responsável: Julia Gonçalves Koehne de Castro
Área Temática:
Versão: 1
CAAE: 47725815.1.3001.5553
Submetido em: 27/10/2015
Instituição Proponente: Faculdade de Ciências da Saúde da Universidade de Brasília
Situação da Versão do Projeto: Aprovado
Localização atual da Versão do Projeto: Pesquisador Responsável
Patrocinador Principal: Financiamento Próprio

7. APÊNDICE

7.1 APÊNDICE 1

Termo de Consentimento Livre e Esclarecido - TCLE

O (a) Senhor(a) _____
_____ está sendo convidado(a) a participar do projeto "Espessura e qualidade da cortical óssea mandibular avaliada por tomografia computadorizada de feixe cônico em mulheres na pós-menopausa e homens acima de 60 anos com e sem osteoporose" desenvolvido sob a responsabilidade da pesquisadora responsável Julia Gonçalves Koehne de Castro e de seu professor orientador André Ferreira Leite.

O objetivo desta pesquisa é comparar a espessura da cortical óssea mandibular em indivíduos com e sem osteoporose. A osteoporose é caracterizada pela redução da densidade óssea e procura-se saber como o osso cortical da mandíbula é afetado pela doença. Para isso, o senhor (a) passará por uma avaliação radiográfica em um aparelho de tomografia computadorizada de uso odontológico a fim de obter imagens da mandíbula. As imagens adquiridas serão analisadas por um profissional especializado e qualquer alteração da normalidade encontrada em seus exames radiográficos será informada. A dose de radiação envolvida nos exames de raios X, principalmente em técnicas digitais, é bem pequena. Quando utilizados de forma indevida, os raios X podem causar efeitos deletérios e irreversíveis à saúde. Porém, os exames radiográficos odontológicos emitem doses de radiação pequenas e controláveis, e o exame somente será realizado mediante o uso de avental de chumbo para proteção individual. Após a aquisição das imagens, o seu exame será avaliado por três radiologistas experientes que farão as medidas da sua cortical óssea duas vezes, com intervalo de um mês.

O(a) senhor(a) receberá todos os esclarecimentos necessários antes e no decorrer da pesquisa e lhe asseguramos que seu nome não aparecerá, sendo mantido o mais rigoroso sigilo através da omissão total de quaisquer informações que permitam identificá-lo(a).

A sua participação será na data _____ com um tempo estimado de 30 minutos para sua realização. Informamos que o(a) Senhor(a) pode se recusar a responder (ou participar de qualquer procedimento) qualquer questão que lhe traga constrangimento, podendo desistir de participar da pesquisa em qualquer momento sem nenhum prejuízo para o(a) senhor(a). Sua participação é voluntária, isto é, não há pagamento por sua colaboração.

Os resultados da pesquisa serão divulgados em meio acadêmico, podendo ser publicados posteriormente. Os dados e materiais utilizados na pesquisa ficarão sob a guarda do pesquisador por um período de no mínimo cinco anos, após isso poderão ser destruídos.

Segundo a Resolução 466/12 do Conselho Nacional de Saúde, o respeito devido à dignidade humana exige que toda pesquisa se processe após consentimento livre e esclarecido e, no caso de crianças e adolescentes ou legalmente incapaz também do assentimento dos sujeitos, indivíduos ou grupos que por si e/ou por seus representantes legais manifestem a sua anuência à participação na pesquisa. Essa mesma resolução garante ao participante de pesquisa alguns direitos, sendo destacados dentre eles o direito de indenização e o direito de ressarcimento:

> II.7 - indenização - cobertura material para reparação a dano, causado pela pesquisa ao participante da pesquisa;

II.21 - ressarcimento - compensação material, exclusivamente de despesas do participante e seus acompanhantes, quando necessário, tais como transporte e alimentação;

Se o(a) Senhor(a) tiver qualquer dúvida em relação à pesquisa, por favor telefone para a pesquisadora Julia Gonçalves Koehne de Castro, telefone: (61) 81911849, e-mail: julia.koehne@gmail.com. Serão aceitas ligações a cobrar.

Este projeto foi Aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Ciências da Saúde (CEP/FS) da Universidade de Brasília - Campus Universitário Darcy Ribeiro- Faculdade de Ciências da Saúde - Asa Norte - DF. O CEP é composto por profissionais de diferentes áreas cuja função é defender os interesses dos participantes da pesquisa em sua integridade e dignidade e contribuir no desenvolvimento da pesquisa dentro dos padrões éticos. As dúvidas com relação à assinatura do TCLE ou os direitos do participante da pesquisa podem ser obtidos através do telefone: (61) 3107-1947 ou do e-mail cepfs@unb.br ou cepfsunb@gmail.com, horário de atendimento de 10:00hs às 12:00hs e de 13:30hs às 15:30hs, de segunda a sexta-feira.

Este documento foi elaborado em duas vias, uma ficará com o pesquisador responsável e a outra com o senhor(a). Todas as folhas do TCLE deverão ser rubricadas pelo(a) senhor(as) responsável e pelo pesquisador responsável.

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Nome / assinatura

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Pesquisador Responsável
Nome e assinatura

Brasília, ___ de _____de _____

7.2 APÊNDICE 2

Clinical Oral Investigations
https://doi.org/10.1007/s00784-019-03193-4

ORIGINAL ARTICLE

A new cone-beam computed tomography–driven index for osteoporosis prediction

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Received: 3 October 2019 / Accepted: 27 December 2019

Abstract

Objective To verify whether mandibular cortical analyses accurately distinguish postmenopausal women with normal bone mineral density (BMD) from women with osteoporosis by means of a cone-beam computed tomography (CBCT)–driven composite osteoporosis index (three-dimensional mandibular osteoporosis index—3D MOI).

Material and methods The comparison was performed between 52 women with normal BMD and 51 women with osteoporosis according to dual-energy X-ray absorptiometry (DXA) examination of the lumbar spine and hip. Mandibular cortical width (MCW) and cortical quality were evaluated on cross-sectional and panoramic reconstructed images. ANOVA, ROC curves and accuracy measurements were used for statistical analyses, as well as a predictive model combining the quantitative and qualitative analyses and age.

Results All CBCT-driven measurements presented good to moderate intra- and interobserver agreements. MCW values were significantly lower in women with osteoporosis. Postmenopausal women with osteoporosis were 8 times more likely to have the cortex classified as C3, and 2.4 times more likely to have MCW thinner than 2.75 mm. The area under the ROC curve was 0.8 for the predictive model.

Conclusions The newly developed 3D MOI enables distinguishing women with osteoporosis from those with normal BMD with good sensitivity and specificity.

Clinical relevance Whenever a CBCT scan is performed for specific clinical indications, a 3D MOI may be performed to qualitatively and quantitatively assess the condition of the mandibular cortex. This may be surely helpful to assess the osteoporosis status in the ageing population and more specifically in peri- or postmenopausal women.

Keywords Cone-beam computed tomography · Osteoporosis · Bone density · Sensitivity and specificity

Introduction

Osteoporosis is a skeletal disease characterised by reduction of bone strength, which in turn creates a predisposition for minimal trauma fractures, also known as fragility fractures. This disease has a high economic and social impact on the worldwide population, due to the high costs related to the treatment of fragility fractures. Bone mineral density (BMD) and bone quality are the main determinants of bone strength, and generally the diagnosis of osteoporosis is based on BMD measurements by means of dual-energy X-ray absorptiometry (DXA) [1, 2]. However, a low availability of DXA limits its routine use in population screening and efforts should be made to identify low BMD individuals, especially those who are at a higher risk of fractures. Therefore, different imaging exams

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Published online: 07 January 2020

7.3 APÊNDICE 3

Imaging Science in Dentistry 2022
https://doi.org/10.5624/isd.20210172

Fractal dimension analysis on CBCT scans for detecting low bone mineral density in postmenopausal women

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ABSTRACT

Purpose: The aim of this study was to compare the fractal dimension (FD) measured at 2 bone sites (second cervical vertebra and mandible) on cone-beam computed tomography (CBCT). The research question was whether FD could serve as an accessory tool to refer postmenopausal women for densitometric analysis. Therefore, the reliability and accuracy of FD were evaluated.

Materials and Methods: In total, 103 postmenopausal women were evaluated, of whom 52 had normal bone mineral density and 51 had osteoporosis, according to dual X-ray absorptiometry of the lumbar spine and hip. On the CBCT scans, 2 regions of interest were selected for FD analysis: 1 at the second cervical vertebra and 1 located at the mandible. The correlations between both measurements, intra- and inter-observer agreement, and the accuracy of the measurements were calculated. A P value less than 0.05 was considered to indicate statistical significance for all tests.

Results: The mean FD values were significantly lower at the mandibular region of interest in osteoporotic patients than in individuals with normal bone mineral density. The areas under the curve were 0.644 ($P=0.008$) and 0.531 ($P=0.720$) for the mandibular and vertebral sites, respectively.

Conclusion: FD at the vertebral site could not be used as an adjuvant tool to refer women for osteoporosis investigation. Although FD differed between women with normal BMD and osteoporosis at the mandibular site, it demonstrated low accuracy and reliability. ***(Imaging Sci Dent 20210172)***

KEY WORDS: Osteoporosis; Cone-Beam Computed Tomography; Fractals; Dual-Energy X-ray Absorptiometry

Introduction

Osteoporosis is a common skeletal disease characteri-zed by compromised bone strength that predisposes individuals to fractures caused by minimal trauma, also known as fragility fractures. There are 2 main properties that relate to bone strength: bone mineral density (BMD) and bone quality.[1] Osteoporosis is a major public health concern due to the social and economic burden caused by fragility fractures. This disease mostly affects the elderly population and postmenopausal women. The costs associated with this disease have tended to rise with population aging.[2,3] Hence, it is very important to identify low-BMD individuals, especially those who are at a higher risk of fractures.[4]

The diagnosis of osteoporosis is generally based on the measurement of BMD, which is routinely determined by dual-energy X-ray absorptiometry (DXA). Even though DXA is considered to be the gold-standard method for the diagnosis of osteoporosis, the examination is not widely available and its effectiveness is limited when evaluating

Received July 7, 2021; Revised October 19, 2021; Accepted October 18, 2021
Published online , 2022
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