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Tese de Doutorado

Parâmetros ósseos para avaliação de baixa densidade mineral óssea e risco de fratura por osteoporose em TCFC de mulheres na pós-menopausa

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Tese apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília, como requisito à obtenção do título de Doutor em Odontologia.

Orientador: André Ferreira Leite

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“Acredite em milagres, mas não dependa deles.”

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Resumo

O presente trabalho teve como objetivo principal analisar parâmetros ósseos mandibulares para avaliação de osteoporose e do risco de fratura em mulheres na pós-menopausa, por meio de tomografia computadorizada de feixe cônico (TCFC). A amostra final foi composta por 103 pacientes, sendo 52 com densidade mineral óssea (DMO) normal e 51 com diagnóstico densitométrico de osteoporose. A mensuração dos índices radiomorfométricos e da dimensão fractal 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 foi significativamente diferente entre mulheres na pós-menopausa com osteoporose e com DMO normal. Mulheres idosas, com a cortical inferior da mandíbula com espessura inferior a 2,75mm na TCFC e classificadas como C3 devem ser investigadas para osteoporose. O segundo artigo avaliou o parâmetro trabecular dimensão fractal em dois sítios distintos (mandíbula e segunda vértebra cervical). Apesar dos valores de dimensão fractal na mandíbula terem sido menores nos pacientes com osteoporose quando comparados aos das mulheres com DMO normal, a análise não apresentou boa reprodutibilidade e acurácia para predizer o diagnóstico densitométrico. Por fim, o terceiro artigo analisou a relação entre a densidade mineral óssea (DXA), o risco de fratura calculado pela ferramenta FRAX e dados de microarquitetura óssea. Neste último estudo, dados de microarquitetura óssea (MAO) foram analisadas pelo programa CT Analyzer, com a seleção de um volume de interesse nas regiões de segunda vértebra cervical e anteriormente ao forame mentual. As análises foram realizadas em TCFCs de 100 mulheres na pós-menopausa e, destas, 46 também responderam à ferramenta FRAX. O parâmetro número de trabéculas correlacionou-se com os dados densitométricos e com o FRAX em ambos os sítios de interesse. A área abaixo da curva foi de 0.732 para predizer o alto risco de fratura no quadril considerando o ponto de corte do FRAX brasileiro de 3%. Na coluna vertebral, o parâmetro espessura das trabéculas e a anisotropia também se correlacionaram com a DMO e com o FRAX. Como conclusão final destes estudos, a TCFC demonstrou acurácia para predizer o diagnóstico densitométrico de osteoporose, com base em um novo índice tridimensional baseado na análise da cortical mandibular, conforme descrito no primeiro artigo. Por outro lado, a análise da dimensão fractal não demonstrou boa acurácia e reprodutibilidade para a mesma finalidade, conforme evidenciado no artigo 2. Já os parâmetros trabeculares, avaliados de forma tridimensional, como o número e a espessura das trabéculas e anisotropia apresentaram correlação com os resultados do DXA e com o FRAX. O parâmetro número de trabéculas apresentou potencial para predizer o risco de fratura baseado nos pontos de corte do FRAX.

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

Abstract

The present work aimed to analyze mandibular bone parameters for evaluating osteoporosis and fracture risk in postmenopausal women, by means of Cone-Beam Computed Tomography (CBCT). The final sample consisted of 103 patients, 52 with normal BMD and 51 with osteoporosis. The measurement of radiomorphometric indices and fractal dimension was performed using ImageJ software. The first article qualitatively and quantitatively evaluated the mandibular cortical bone. 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. Elderly women with inferior mandibular cortical thickness lower than 2.75 mm on CBCT and classified as C3 should be investigated for osteoporosis. The second article calculated fractal dimension in two different sites (mandible and second cervical vertebra). Although the fractal dimension values in the mandible were lower in patients with osteoporosis when compared to those of women with normal BMD, the analysis did not present good reproducibility and accuracy to predict the densitometric diagnosis. Finally, the last article aimed to analyze the relationship between bone mineral density (DXA results), fracture risk calculated by FRAX tool and bone microarchitecture data. In the third study, bone microarchitecture data were analyzed by the CT Analyzer program, with the selection of two volume of interests in the regions of the second cervical vertebra and anterior to the mental foramen. The analyses were performed on CBCT scans of 100 postmenopausal women and, from these, 46 also responded to the FRAX tool. The bone parameter number of trabeculae correlated with densitometric data and with FRAX at both sites of interest. The trabecular number assessed in the mandible showed the most promising results in comparison to the other variables, since it presented a strong inverse correlation both for hip fractures and major osteoporotic fractures. The area under the curve value was 0.732 for predicting high hip fracture risk by using the Brazilian FRAX cut-off. In the spine, bone parameter trabecular thickness and anisotropy also correlated with BMD and FRAX. As a final conclusion of the three studies, CBCT showed accuracy to predict the densitometric diagnosis of osteoporosis, based on a new cortical index (3D MOI), as described in the first article. On the other hand, the analysis of fractal dimension did not demonstrate good accuracy and reproducibility for the same purpose, as shown in article 2. Some 3D trabecular parameters, such as the number and thickness of trabeculae and anisotropy were correlated with DXA and FRAX results, and the trabecular number at the mandibular site may be further investigated as potential tool to predict fracture risk, as shown in article 3.

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

Lista de Abreviaturas e Siglas

Capítulo 1

DMO – Densidade mineral óssea
DXA – Densitometria óssea por dupla emissão de raios X
MAO – Microarquitetura óssea
VOI – Volume de interesse
MicroCT – Microtomografia computadorizada
TCFC – Tomografia computadorizada de feixe cônico
FOV – Campo de visão
TCFL – Tomografia computadorizada de feixe em leque
FRAX – Fracture Risk Assessment Tool

Capítulo 2

BMD – Bone mineral density
CBCT – Cone-beam computed tomography
3D MOI – Tridimensional mandibular index
DXA – Dual-energy x-ray absorptiometry
MCW – Mandibular cortical width
CS – Cross-sectional
PR – Panoramic image
3D MOI PR – Panoramic reconstruction image
3D MOI CS – Cross-sectional images
3D MOI CQ - qualitative measure assessing cortical bone quality

Capítulo 3

FD – Fractal dimension
CBCT – Cone-beam computed tomography
BMD – Bone mineral density
DXA - Dual x-ray absorptiometry
VOI – Volume of interest
ROI – Region of interest
ROI-v – Region of interest in the second cervical vertebra
ROI-m – Regio of interest anterior to the mental foramen
FN – Femoral neck
TH – Total hip

Capítulo 4

OP - Osteoporosis
DXA - Dual x-ray absorptiometry
BMD - Bone mineral density
TBM – Trabecular bone microarchitecture

CBCT - Cone beam computed tomography
FRAX - Fracture Risk Assessment Tool
FOV – Field of view
ROI - Region of interest
ROI1 – Region of interest in the second cervical vertebra
ROI2 - Region of interest in anterior to the mental forame

SUMÁRIO

CAPÍTULO 1 - INTRODUÇÃO, REVISÃO DA LITERATURA E OBJETIVOS

1.1 INTRODUÇÃO

A osteoporose é uma doença com impacto mundial que causa diminuição na resistência óssea. A resistência óssea reflete-se pela integração entre a densidade mineral óssea (DMO) e a qualidade óssea [1]. A fragilidade do osso ocasionada pela doença predispõe ao aumento da ocorrência de fraturas por trauma mínimo, a consequência principal da doença, caracterizadas por fraturas em quedas da própria altura ou fraturas que não ocorreriam em situação de normalidade. As fraturas representam a consequência principal da doença, causando aumento na morbimortalidade e grande impacto socioeconômico com o aumento no número de internações. Portanto, um correto e precoce diagnóstico da doença é de fundamental importância para a saúde pública [2-5].

O diagnóstico da osteoporose em geral se dá pela análise da DMO obtida pelo exame de densitometria óssea por dupla emissão de raios X (DXA) [6]. No entanto, como a DMO é apenas um dos fatores envolvidos na resistência óssea, muitos indivíduos com DXA óssea normal têm o seu diagnóstico da doença apenas após a ocorrência das fraturas por trauma mínimo. Nestas pessoas, a qualidade do osso está comprometida, o que justifica a fragilidade óssea [7]. Torna-se necessário, portanto, o rastreamento de indivíduos com a doença e com risco aumentado de fratura.

Diversos estudos prévios demonstraram que alterações na cortical [8-16] e no trabeculado ósseo [16-21] da mandíbula foram capazes de identificar pacientes com osteoporose em radiografias panorâmicas da face, utilizando o exame de DXA como padrão-ouro para a identificação da doença. Os estudos com tomografia computadorizada de feixe cônico (TCFC) foram mais escassos na cortical [21-25] e, principalmente, no trabeculado ósseo [23-24], com resultados controversos para o osso trabecular. Todavia, esses estudos de TCFC utilizaram distintas metodologias, com amostras mais reduzidas. Não foram encontrados estudos prévios que avaliaram a relação entre os parâmetros ósseos mandibulares em TCFC e o risco de fratura. Pelo fato de a TCFC ser bastante utilizada na população idosa, principalmente para o planejamento de implantes dentários, torna-se necessário verificar a acurácia de

mensurações nestas imagens para identificar a população com maior risco para osteoporose e fraturas por trauma mínimo.

As carências na literatura acima mencionadas justificam o presente trabalho, que tem como objetivo principal analisar parâmetros ósseos mandibulares para identificação de osteoporose e de risco de fratura em TCFC de mulheres na pós-menopausa. Além da revisão da literatura, serão apresentados os três artigos gerados desta tese, sendo dois já publicados em revistas indexadas e o outro em fase de conclusão para submissão.

1.2 REVISÃO DA LITERATURA

A osteoporose é uma doença esquelética que causa diminuição na resistência óssea, predispondo a um maior risco de fratura. Duas propriedades principais estão relacionadas à resistência óssea: a DMO e a qualidade óssea [1]. Alterações nestas propriedades causam uma deterioração microestrutural na arquitetura óssea, que justificam a etimologia da palavra “osso poroso”. Esta diminuição da resistência aumenta a fragilidade do osso e o predispõe a fraturas por trauma mínimo [3].

As fraturas por fragilidade óssea, também conhecidas por fraturas por trauma mínimo são aquelas nas quais o osso fratura após um impacto de baixo nível que, normalmente, não iria quebrar um “osso normal”. Na avaliação do paciente, quando este relata uma queda da própria altura, existe o forte indicativo que esta fratura tenha ocorrido pela presença da doença [4].

Aproximadamente 200 milhões de pessoas possuem osteoporose e aproximadamente nove milhões de fraturas são causadas pela doença, significando quase uma fratura por trauma mínimo a cada três segundos. Uma pessoa que teve uma fratura relacionada à osteoporose possui um risco muito aumentado de outra fratura por trauma mínimo ao longo da vida [27]. Estas fraturas ocorrem principalmente no quadril, vértebra e antebraço. As fraturas geram um alto impacto socioeconômico na sociedade. Um estudo europeu apontou um custo aproximado de 37 bilhões de euros por ano relacionado às fraturas por trauma mínimo e este custo tende a aumentar 23% até o ano de 2030. Em relação ao impacto social, as fraturas estão associadas com significativa morbidade, mortalidade e reduzida qualidade de vida, relacionada não somente às fraturas, mas às comorbidades encontradas nestes pacientes de risco [3, 28, 29]. Fraturas de quadril são as mais preocupantes, gerando um aumento de mortalidade em 20% nos dois anos após a ocorrência e com 50% das mulheres acometidas necessitando de assistência para a realização de atividades cotidianas [30].

Visto que o osso se torna mais frágil e poroso com a idade, a idade avançada é um fator de risco significativo para a doença e também mais prevalente na população feminina, visto que a queda dos níveis de estrogênio pós-menopausa está

relacionada à perda da massa óssea. O risco de fratura aumenta, portanto, significativamente com a idade. Com o envelhecimento da população mundial e aumento da expectativa de vida, a ocorrência da osteoporose e respectivas fraturas por trauma mínimo tendem a aumentar significativamente [5].

Estima-se que, em 2050, 23% dos brasileiros terão mais de 60 anos. De acordo com o Instituto Brasileiro de Geografia e Estatística (IBGE), a população brasileira que possui mais de 60 anos representa hoje 14,66% da população brasileira. Sendo assim, de 2022 a 2050, o aumento da faixa etária acima dos 60 anos consistirá em 57% [30]. Com o envelhecimento da população espera-se um aumento considerável na ocorrência de osteoporose e de outras doenças crônicas [31]. Os custos associados com a doença aumentarão com o envelhecimento da população, assim como os impactos sociais da doença. Logo, é fundamental identificar indivíduos com baixa DMO e com risco mais alto para fraturas [32-34].

O diagnóstico da osteoporose é geralmente baseado na mensuração da DMO por meio da DXA [6]. A densitometria óssea é um exame considerado padrão ouro pela literatura e o diagnóstico final da doença é feito pelo seu resultado, com a conjugação de alguns achados clínicos [35]. A DXA é rápida, indolor e segura, já que esta emite doses muito baixas de radiação, podendo ser repetida ao longo dos anos. Os sítios mais utilizados para avaliação da DMO são a coluna vertebral e do fêmur/quadril. Enquanto a região vertebral representa mais o esqueleto axial, com predominância de osso trabecular, a região femoral representa o esqueleto apendicular, com predominância de osso cortical [36]. Nesse sentido, o resultado do exame torna-se mais fidedigno da condição esquelética do paciente.

O resultado do exame de DXA é dado por meio do T-Score e o Z-Score. O T-Score é utilizado para comparar o resultado obtido com uma população jovem e saudável. Os seguintes valores são utilizados como referência para o diagnóstico: T-Score de pessoa com DMO normal – acima de -1; T-Score de pessoa com osteopenia – entre -1 e -2,5; T-Score de pessoa com osteoporose – abaixo de -2,5. Já o Z-Score é usado para comparar o resultado obtido com um valor esperado baseado em gênero e idade. Este é mais empregado em resultados de crianças e adolescentes [37].

Por conta da ausência de sintomatologia no decorrer do curso clínico, a osteoporose é considerada como uma doença silenciosa, muitas vezes diagnosticada apenas após a ocorrência das fraturas. Ainda que o exame de DXA seja considerado como o padrão-ouro para o diagnóstico da doença, o exame não é amplamente disponível e sua efetividade é limitada para avaliação de alteração da qualidade óssea. Muitos pacientes com DMO normal no exame densitométrico são acometidos por fraturas por trauma mínimo [34, 38-39].

Estima-se que quase 50% da resistência óssea está relacionada à qualidade do osso e não somente à densidade deste [40]. Nesse sentido, mais que o diagnóstico precoce da doença, o rastreamento dos pacientes com maior risco para fratura e a identificação de alterações ósseas microestruturais que afetam a qualidade do osso são estratégias mais eficazes para o enfrentamento da consequência mais grave da osteoporose que é a fratura [34, 41].

A DXA proporciona uma DMO aparente bidimensional projetada que não capta a heterogeneidade da composição do tecido ósseo e as macro, micro e nano estruturas críticas para a sua resistência. A avaliação da base estrutural da fragilidade óssea tem se concentrado principalmente no osso trabecular com base na ocorrência comum de fraturas de fragilidade em locais com quantidades substanciais de osso trabecular. Além disso, o osso trabecular possui um metabolismo oito vezes maior que o osso cortical e, portanto, as perdas ósseas costumam se iniciar neste tipo de osso, previamente ao comprometimento do osso cortical [42]. A microarquitetura óssea está relacionada, portanto, à estrutura do osso e a sua geometria, [43]. Algumas teorias sugerem que o osso sofre mudanças ao longo do tempo, como diz a lei de Wolf, que define a adaptação do osso dependendo dos estímulos, para melhorar a sua resistência [44].

Por outro lado, mais de 75% do esqueleto é composto por osso cortical. De todas as fraturas por osteoporose/trauma mínimo, aproximadamente 80% são apendiculares e envolvem regiões ricas em osso cortical e cerca de 70% de toda a perda óssea apendicular relacionada à idade é cortical e se deve principalmente ao desequilíbrio de remodelação intracortical que aumenta a porosidade cortical. A falha em atingir o pico ideal da microestrutura óssea durante crescimento devido a doenças

e a deterioração do osso cortical e trabecular produzido pela perda óssea comprometem a resistência óssea.

Estudos prévios avaliaram a influência da análise da MAO na resistência óssea por meio de suas propriedades mecânicas [45,46]. Para uma boa compreensão da osteoporose, é necessário levar em consideração os conceitos de remodelação óssea. Independente de idade, existem os processos de reabsorção e de formação óssea, nos quais a atuação dos osteoclastos e osteoblastos, respectivamente, são fundamentais. A manutenção da resistência óssea está diretamente relacionada a esta remodelação, já que é nela que ocorre a substituição de osso antigo e danificado [47,48]. Mulheres na pós-menopausa ficam mais susceptíveis ao desenvolvimento da doença, devido, principalmente, a alterações hormonais e idade [49]. Após a menopausa, ocorre um desequilíbrio nestes processos, a reabsorção óssea pode se sobrepor à formação do tecido ósseo, diminuindo a resistência óssea e em consequência o risco de fratura. Este desequilíbrio gera alterações microestruturais no tecido ósseo acometido [50].

A perda de resistência óssea produzida pela deterioração microestrutural é desproporcional à perda óssea que produz esta deterioração [42]. A razão para isso é que a perda de força aumenta como uma sétima função de potência do aumento da porosidade cortical e uma terceira função de potência de queda na densidade trabecular [51], daí a necessidade de quantificar a microestrutura óssea tanto do osso cortical quanto do osso trabecular.

Alguns autores demonstraram que afilamentos na cortical mandibular e aumento da porosidade podem ser vistas em mulheres na pós-menopausa e em homens idosos com baixa DMO ou osteoporose. Estas alterações foram evidenciadas principalmente em radiografias panorâmicas da face [8-16, 52]. Existem também estudos prévios que avaliaram o osso trabecular neste tipo de exame de imagem, porém com maior diversidade de abordagens metodológicas e resultados muitas vezes controversos [16-21]. Apesar de ter uma excelente utilização, principalmente como exame de triagem e para tarefas diagnósticas de rotina na prática clínica, nem todas as estruturas investigadas podem ser observadas completamente em exames bidimensionais, como as radiografias panorâmicas [53]. Além disso, a avaliação microestrutural do osso pode não ser possível em um exame bidimensional [43]. As

radiografias panorâmicas nos oferecem uma visão ampla de alterações ósseas, no entanto a TCFC oferece uma relação de profundidade, dimensão e relação com estruturas anatômicas mais precisa [54].

Desde a sua introdução no mercado, há mais de duas décadas, a TCFC já demonstrou ampla aplicação na odontologia, superando algumas limitações relacionadas à sobreposição de imagem e distorções inerentes aos exames bidimensionais. Hoje, o seu uso já faz parte do cotidiano clínico e da pesquisa, com mais de 279 diferentes equipamentos de TCFC catalogados no mercado desde o seu surgimento [55]. No entanto, apesar de sua ampla utilização atualmente, os estudos que analisaram as alterações ósseas corticais [21-25] e trabeculares [23-24] relacionadas à baixa DMO são mais escassos, sendo que a acurácia e a reprodutibilidade das mensurações em TCFC não foram analisadas ou possuem resultados controversos.

Ao se tratar de exames de imagem para avaliar osso trabecular, o principal exame apontado na literatura é a microtomografia computadorizada (MicroCT) [56], porém esta também possui algumas limitações, sendo a principal delas a necessidade de a amostra ser *ex vivo* quando se trata de seres humanos [57]. Uma alternativa boa relatada por estudos recentes é o uso da TCFC para avaliação do osso trabecular. Os estudos mencionam a possibilidade de empregar exames com aparelhos de TCFC de alta resolução e campo de visão (FOV) pequeno para a análise da MAO na mandíbula [57-59] e no punho [60]. Medidas relacionada à MAO como anisotropia [59], índice de modelo estrutural [44], dimensão fractal [23-24] e outros parâmetros estruturais trabeculares [61,62] têm sido objetos de estudo em exames de TCFC.

A utilização de exames de TCFC para analisar a MAO pode ser útil, mas por si só, ainda não indicam o risco de fratura. Existem algumas ferramentas para predizer o risco de fratura com base em fatores de risco como a Fracture Risk Assessment Tool (FRAX), QFracture e Garvan Fracture Risk Calculator [63-65]. A FRAX é uma ferramenta mais amplamente utilizada e validada para diversos países no mundo, incluindo o Brasil [63-67]. O algoritmo FRAX foi criado na universidade de Sheffield na Inglaterra e foi lançada em 2008 pela Organização Mundial de Saúde (OMS). O algoritmo usado na ferramenta é alimentado com informações do paciente como idade, gênero, peso, altura, e DMO do colo femoral. Na ferramenta há espaço para

coleta de dados dicotômicos relacionados ao paciente, como 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 [63-65]. A ferramenta tem sido amplamente utilizada no mundo, já que esta realiza, através de um algoritmo específico, análises baseadas na população de cada país. O objetivo da ferramenta é, portanto, juntar todas as informações pertinentes aos fatores de risco para fratura e calcular o risco de fraturas relacionadas à osteoporose (fraturas de quadril e fraturas maiores) no período de 10 anos após o cálculo. Outra vantagem dessa ferramenta é que é possível inserir a DMO do colo femoral como um dos dados, porém não é obrigatório para o cálculo, já que nem todos os pacientes têm acesso a este tipo de exame [63-67]. Segundo estudo conduzido em 2017, apenas um terço dos aparelhos de DXA localizados no Brasil estão à disposição do sistema único de saúde (SUS), sendo que somente 9,6% dos municípios têm um desses aparelhos [68].

Pelo fato de a TCFC ser bastante utilizada na população idosa, principalmente para o planejamento de implantes dentários, torna-se necessário verificar a acurácia de mensurações nestas imagens para identificar a população com maior risco para osteoporose e fraturas por trauma mínimo. Esta revisão da literatura discutiu a escassez de estudos em TCFC que analisaram a acurácia deste exame para predizer o resultado densitométrico de osteoporose. Não foram encontrados estudos prévios que avaliaram a relação entre os parâmetros ósseos mandibulares em TCFC e o risco de fratura. Para avaliar a MAO corretamente, é preciso ter um exame tridimensional, já que a geometria do trabeculado ósseo leva em consideração parâmetros como a espessura, espaço e número de trabéculas [44].

A falta de acesso ao exame de DXA por grande parte da população impossibilita que a maioria tenha um diagnóstico completo e preciso da doença, com orientações adequadas. É senso comum que alguns pacientes costumam procurar tratamentos apenas após algumas ocorrências relacionadas a urgências. Isto conjectura a necessidade de estudar outras formas de avaliar o risco de fratura. E é por isso que existe um potencial e utilidade muito grande em investigar se existe correlação direta do risco de fratura calculado por ferramentas validadas com exames realizados em tratamentos mais rotineiros.

1.3 OBJETIVOS

O objetivo geral deste trabalho foi verificar se parâmetros ósseos analisados em tomografia computadorizada de feixe cônico poderiam identificar mulheres na pós-menopausa com osteoporose e com risco aumento de fratura por trauma mínimo relacionada à doença.

O trabalho teve como objetivos específicos:

- Avaliar a acurácia das análises qualitativa e quantitativa em TCFC da cortical inferior da mandíbula para predizer o diagnóstico densitométrico da osteoporose. Este objetivo específico originou o artigo 1.

- Avaliar a acurácia da análise da dimensão fractal da mandíbula e da coluna vertebral para predizer o diagnóstico densitométrico da osteoporose. Este objetivo específico originou o artigo 2.

- Avaliar a correlação de medidas de MAO (fator do padrão trabecular, índice estrutural de modelo, espessura, número e separação trabecular, dimensão fractal, e anisotropia) e os valores da densitometria óssea e o risco de fratura analisado pelo FRAX. Este objetivo específico originou o artigo 3, ainda não publicado e finalizado.

As metodologias utilizadas para responder estes objetivos específicos estão detalhadas em cada capítulo desta tese/artigo.

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CAPÍTULO 2 - A NEW CONE-BEAM COMPUTED TOMOGRAPHY–DRIVEN INDEX FOR OSTEOPOROSIS PREDICTION

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

2.1 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 indexes [4–12]. Recently, some studies have analyzed 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 with 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.

2.2 METHODS

2.2.1 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 3 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).

2.2.2 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 criterion 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.

2.2.3 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 0.25 mm, 120 kVp, 8 mA, field of view of 8 × 8 cm, and a 40-s scan time. Images were firstly analyzed using the CBCT manufacturer software (Xoran 3.1.62, Xoran Technologies, Ann Arbor, MI, USA).

Cross-sectional (CS) and panoramic images (PR) were re-constructed from all CBCT scans. A “sharpen low 3 × 3” filter was applied to the images for evaluation. The CS and PR were reconstructed by drawing the cutting curve on the center of the axial images in which both mental foramina were most visible (Fig. 1a) [17]. TIFF-format images from all individuals were exported and analyzed using the ImageJ software v1.47 (National Institutes of Health, Bethesda, MD, USA).

2.2.4 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 center 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 10.25 mm.

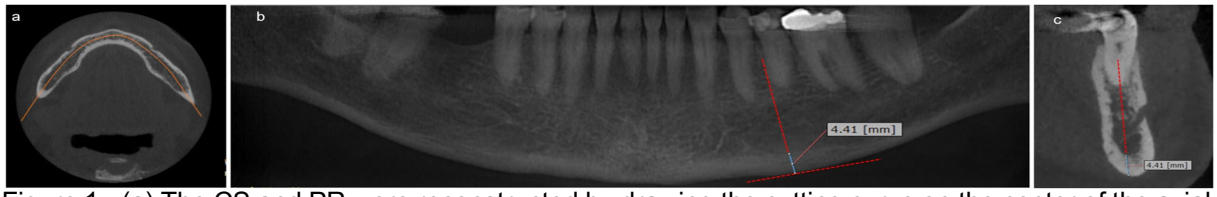

Figure 1 - (a) The CS and PR were reconstructed by drawing the cutting curve on the center of the axial images in which both mental foramina were most visible. (b) Three-dimensional morphometric index on panoramic reconstructed image (3D MOI PR). (c) Three-dimensional morphometric index on cross-section (3D MOI CS)

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).

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. 2 a and b) C2: endosteal margin presenting semilunar defects (lacunar resorption) or appearing to form endosteal residues (Fig. 2 c and d) C3: cortical layer forming heavy endosteal cortical residues and being clearly porous (Fig. 2 e and f) The 3D MOI CQ was considered positive when the cortex was classified as C2 and C3 on at least one CBCT reconstruction (PR or CS).

Images were analyzed independently by two radiologists with more than 10 years of experience with CBCT assessment, already calibrated for mandibular cortical analyses, and blinded for the DXA results, on a 25-in. high-resolution LCD display (2560 × 1440 pixels) in a calm and dim-lit environment. To calculate intraobserver reliability, one observer analyzed the indices twice within 1-week interval. For inter-observer 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).

2.2.5 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 × 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 (2) 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 in- dices (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.

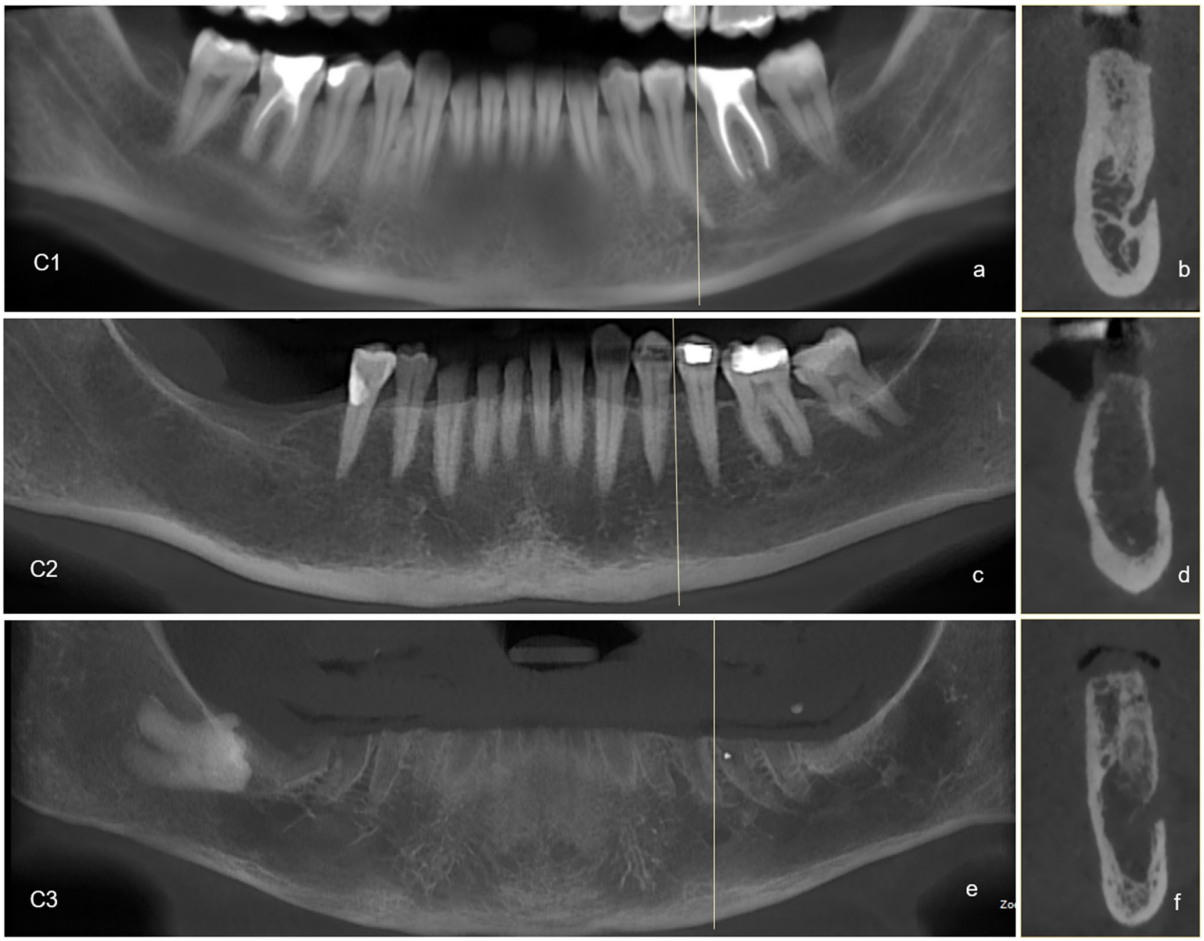

Figure 2 - Scheme of the three-dimensional evaluation of the cortical quality (3D MOI CQ) using CBCT panoramic (a, c and e) and cross-sectional (b, d and f) reconstruction images and classified as: C1 (a and b), C2 (c and d) and C3 (e and f).

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 and 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).

2.3 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 post- menopausal 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)

2.3.1 Reliability of 3D MOI

2.3.1.1 Intra- and interobserver agreements

For the qualitative analysis, a moderate intraobserver agreement was found (kappa = 0.6). Figure 3 a and b 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).

2.3.2 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. 5 a and b, respectively). No association was found between age and 3D MOI CQ, $p = 0.291$ (Fig. 5c).

2.3.3 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). Figure 5 d, e and f 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.

2.3.4 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 2.75 mm was found.

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.

2.4 DISCUSSION

To the best of our knowledge, this is the first diagnostic test study that analyzed the accuracy of both qualitative and quantitative indices 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.

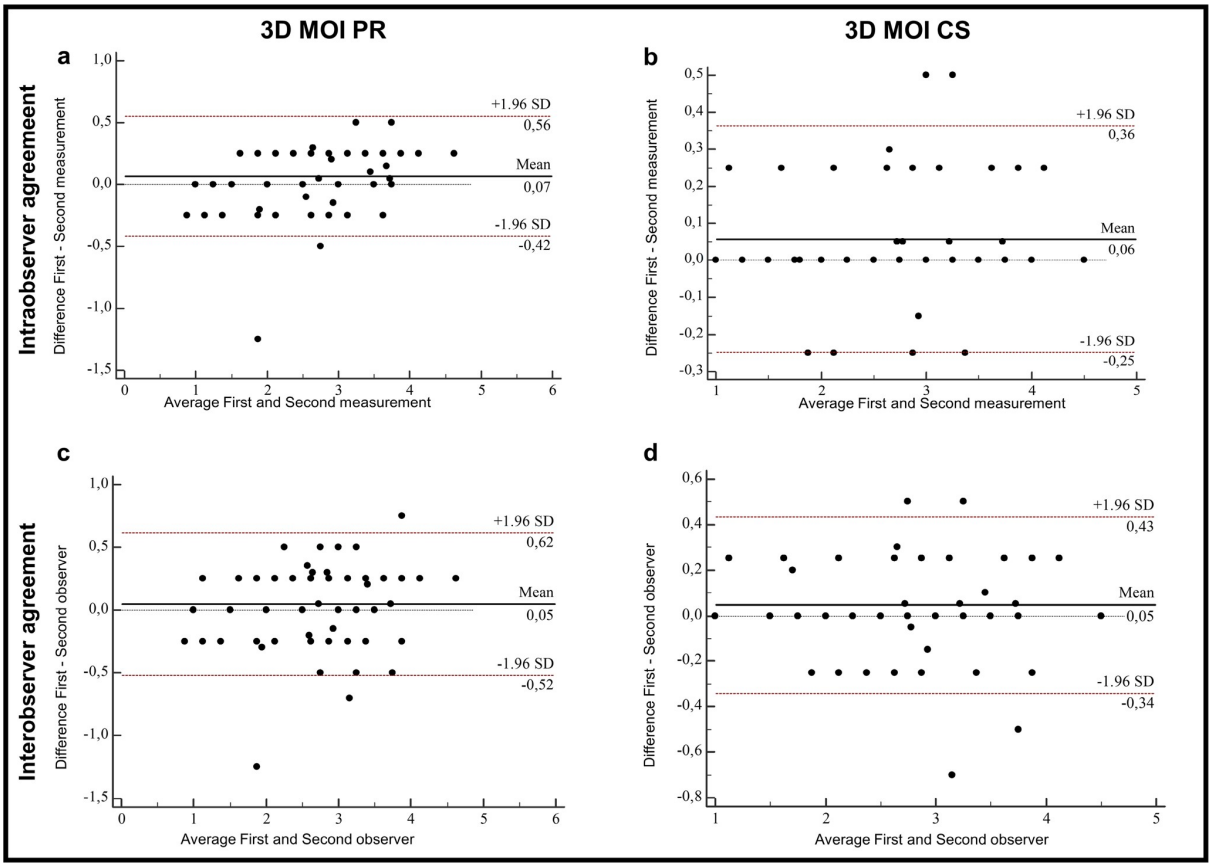

Figure 3 - Bland-Altman plots showing good intra- and interobserver agreements for all the CBCT measurements. (a) Intraobserver agreement for 3D MOI PR. (b) Intraobserver agreement for 3D MOI CS. (c) Interobserver agreement for 3D MOI PR. (d) Interobserver agreement for 3D MOI CS.

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 analyze 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.

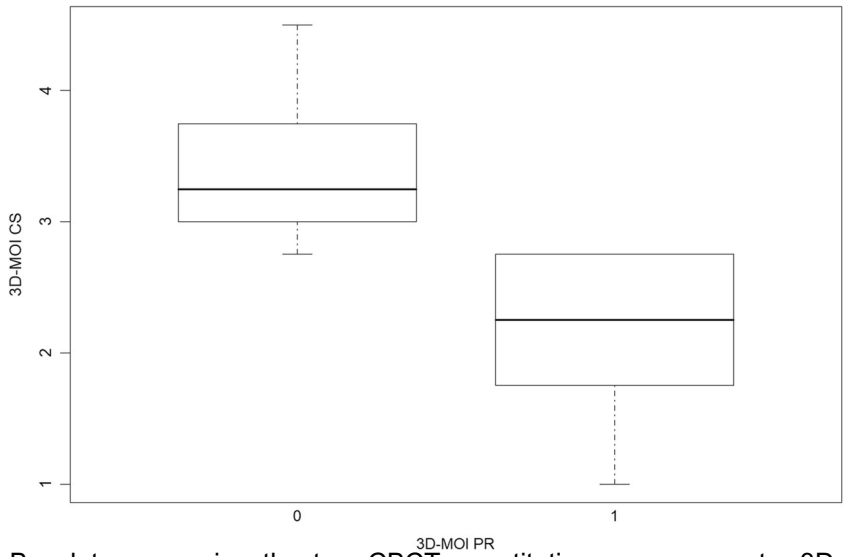

Figure 4 - Boxplots comparing the two CBCT quantitative measurements. 3D MOI CS presented significantly higher values than 3D MOI PR

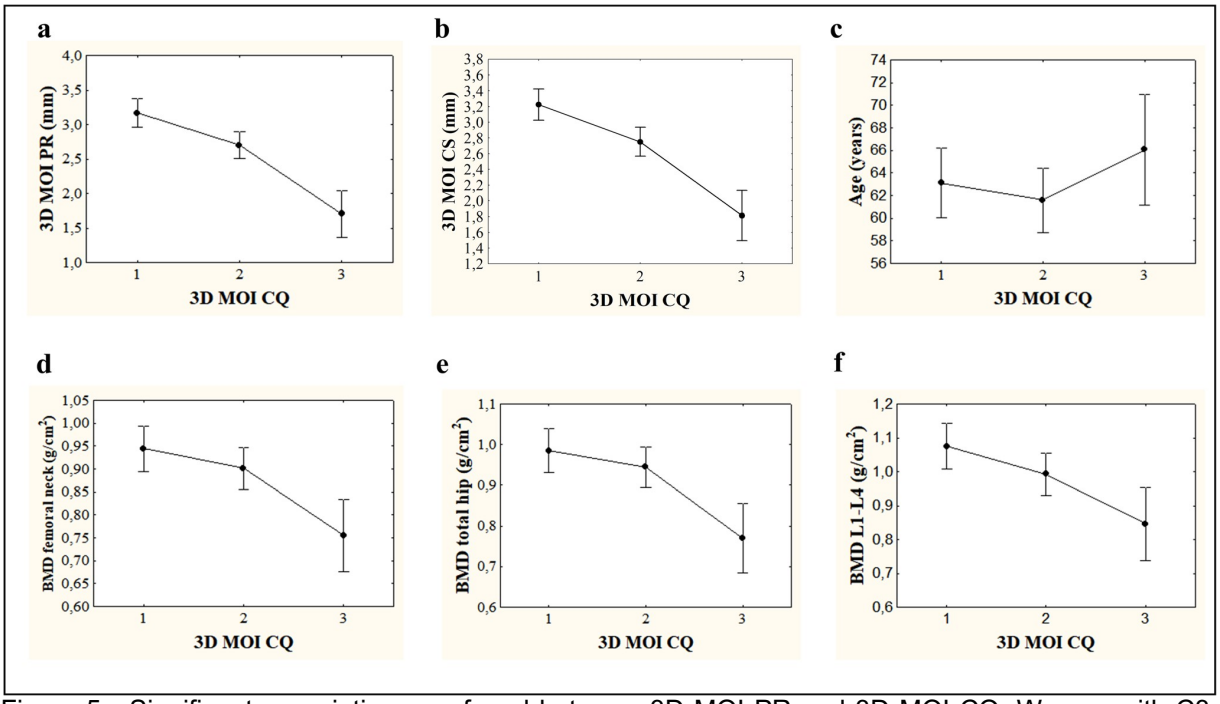

Figure 5 - Significant association was found between 3D MOI PR and 3D MOI CQ. Women with C3 classification presented lower mandibular cortical width values on the CBCT images (a). Significant association was also found between 3D MOI CS and 3D MOI CQ (b). No association was found between age and 3D MOI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

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 3.22 mm ± 0.87 mm, and among women with osteoporosis (21 women) the mean MCW was 2.23 mm ± 0.85 mm [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 analyzed data.

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 (2.75 mm)	3D MOI CS (2.75 mm)	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, LR+ positive likelihood ratio, LR− negative likelihood ratio, AUC area under the curve

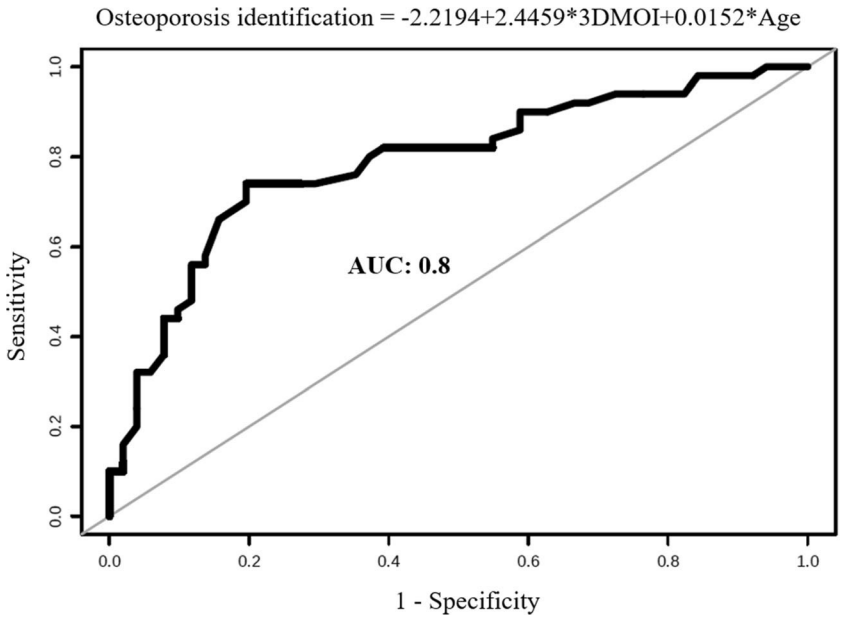

Figure 6 – The predictive mode l for identifying postmenopausal women with osteoporosis combining 3D MOI (qualitative and quantitative analyses) and age. This model was built based on a ROC-curve analysis. The area under the ROC curve was 0.8. The formula of the model is shown on the upper part of the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

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% and the specificity was 62.5% for a slice thickness of 25 mm [17]. These lower values of diagnostic accuracy measurements, when compared with 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 post- menopausal 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 with qualitative cortical mandibular index [28–30]. Concerning MCW on the radiographs, the authors found a cut-off point of 3 mm 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 2.75 mm 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 2.75 mm.

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2.4.1 Compliance with ethical standards

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

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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CAPÍTULO 3 - FRACTAL DIMENSION ANALYSIS ON CBCT SCANS FOR DETECTING LOW BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

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.

3.1 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 indexes, 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 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).

3.2.1 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.

3.2.2 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.

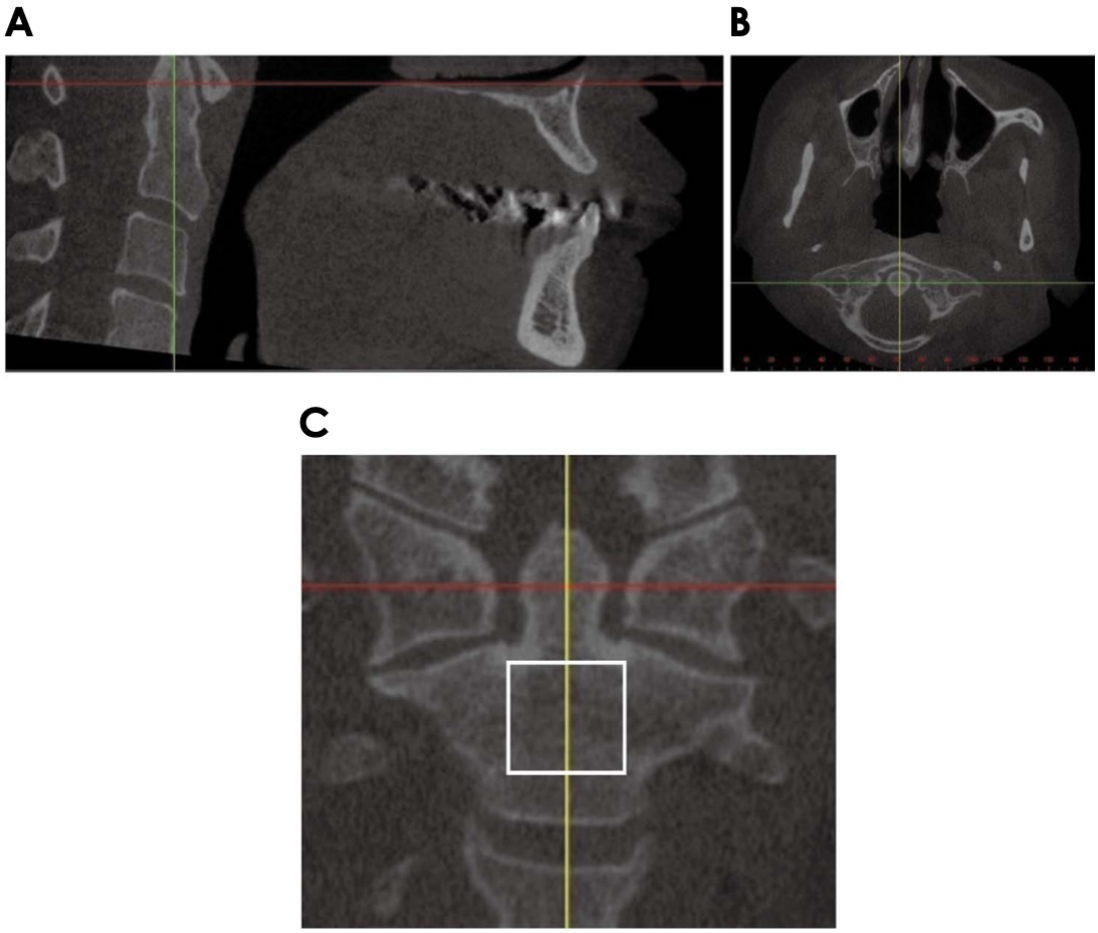

Figure 1 - Slices used for the assessment of the second cervical vertebra, as well as their positions and alignments. This ROI was standardized by calibrating the position of C2. A line was drawn passing through the dens in the sagittal plane (Fig. 1A.) and tilting it perpendicular to the computer screen. 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-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. 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.). 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 3 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.

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.

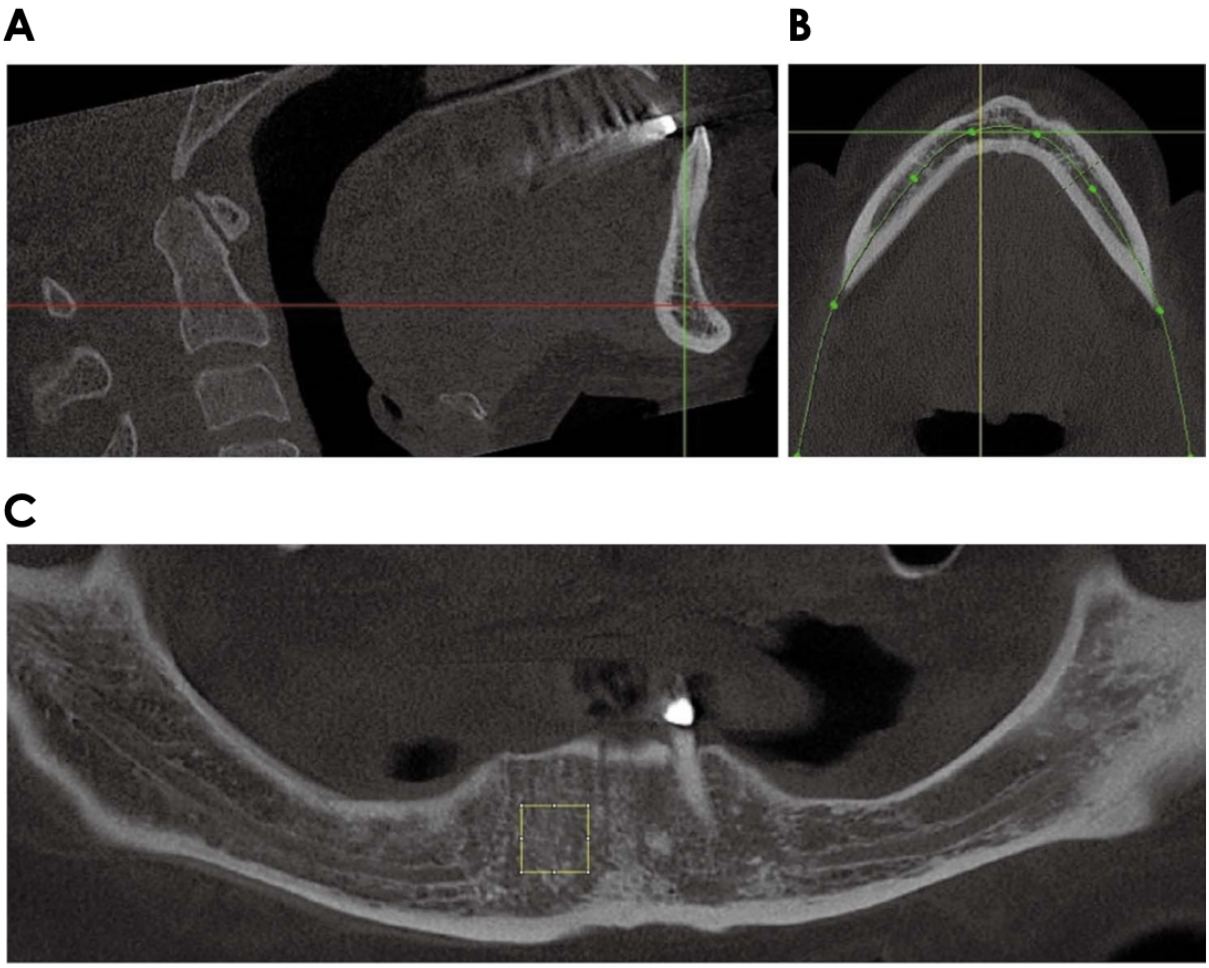

Figure 2 - Images used for assessing the mandible, including their positions and alignments. In the sagittal view (Fig. 2A.) the mental foramen was tilted until it was also perpendicular to the computer screen. The cutting curve was drawn on the center of the axial image of the mandible (Fig. 2B.) in 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).

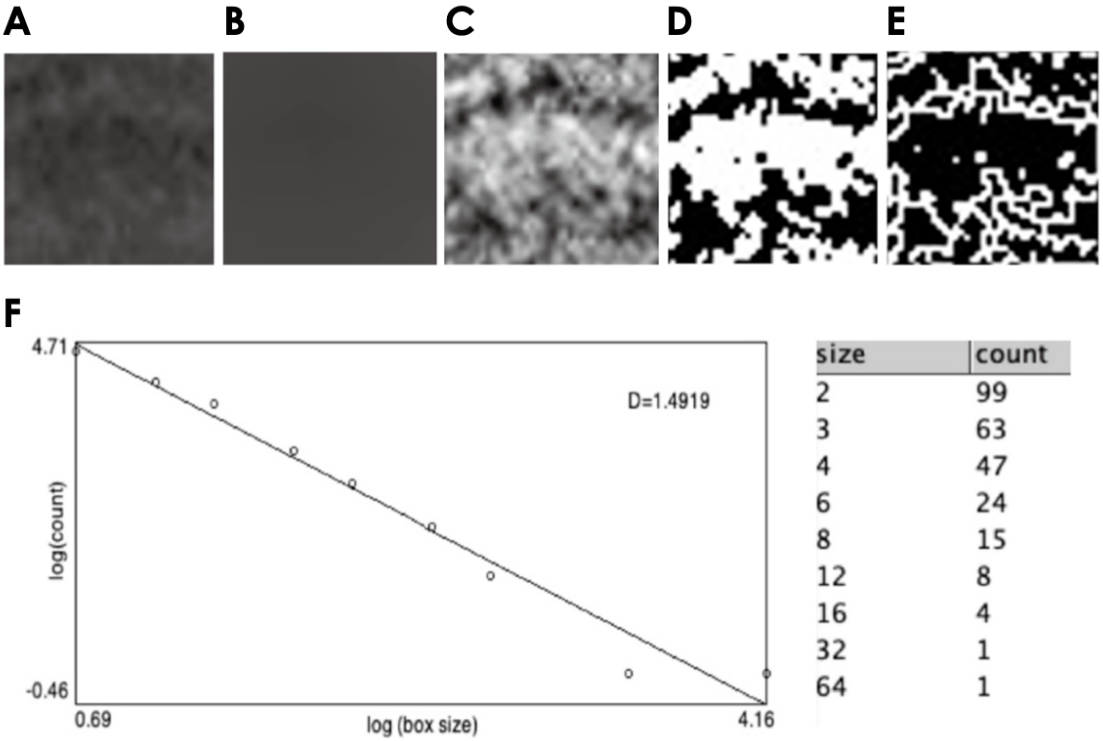

Figure 3. Image processing method for fractal dimension analysis. A. Duplication. B. Gaussian filter at 10.00 pixels. C. Subtraction of the second image from the first. D. Turning image into a binary 8-bit image, E. Skeletonization and outlining the bone trabeculae. F. The box counting procedure and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

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.

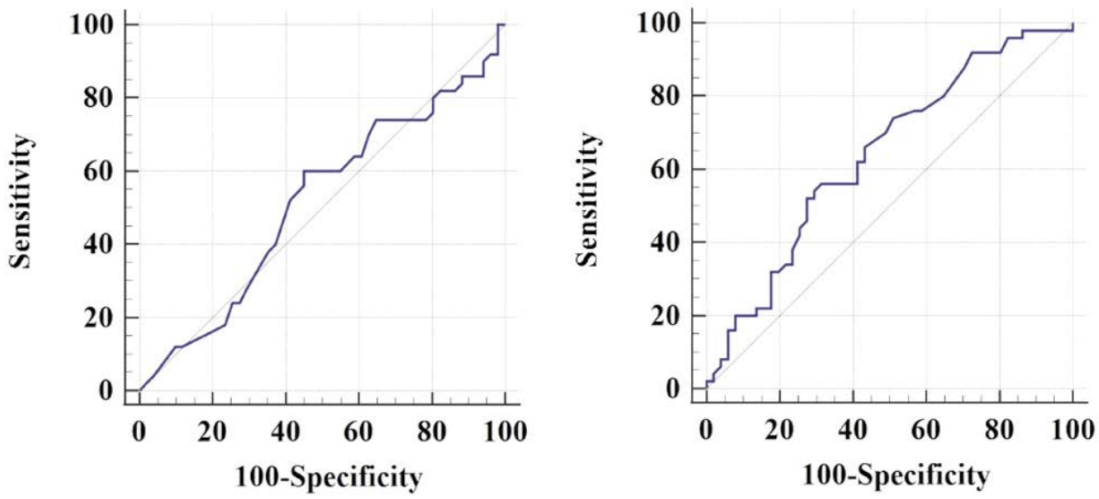

Figure 4 - Receiver operating characteristic (ROC) curves of the fractal dimension analysis at the vertebral (A) and mandibular (B) sites.

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).

3.3 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

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).

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.

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%.

3.4 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 research 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].

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 assessments [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.

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CAPÍTULO 4 – MANDIBULAR AND VERTEBRAL MICROSTRUCTURAL PARAMETERS ON CBCT AND FRAGILITY FRACTURES RISK IN POST-MENOPAUSAL WOMEN

Abstract

Aim: The aim of this study was to assess trabecular bone microarchitecture parameters in postmenopausal women and its correlation with skeletal BMD and fragility fractures risk evaluated by FRAX.

Methodology: In this study, 100 postmenopausal women that had previously underwent dual-energy x-ray absorptiometry (DXA) and cone-beam computed tomography (CBCT) exams were initially selected. Several bone parameters were calculated by selecting two different volumes of interest (VOIs) shaped after a 5x5x5mm cube using CT analyzer software on the CBCT scans, one in the mandible and the other in the second cervical vertebra. The parameters were: trabecular pattern factor, structure model index, trabecular thickness, trabecular number, trabecular separation, fractal dimension, and the degree of anisotropy. From the selected patients, 46 postmenopausal women were interviewed and Fracture Risk Assessment Tool was applied. Hip and major osteoporotic fracture risks were calculated by FRAX and the cut-offs of 3% and 15% were considered for both fracture types, respectively.

Results: FRAX results were associated with lumbar spine and hip BMD. Trabecular number parameter presented a negative correlation with FRAX results considering both hip (r=-0.40) and major osteoporotic fracture risk (r=-0.36). The area under the curve of trabecular number parameter was 0.732 to identify a high hip fracture risk.

Conclusion: Trabecular bone parameters on CBCT can be potentially used as fracture risk predictors, especially trabecular number at the mandibular site.

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

4.1 INTRODUCTION

Osteoporosis is a skeletal disease that causes decrease in bone strength. Bone strength results from the integration between bone mineral density (BMD) and bone quality [1]. Bone fragility predisposes to an increase in the occurrence of osteoporotic fractures where bones can break from low level impact or stress that would not normally break a healthy bone. Fractures represent the main consequence of the disease, especially in elderly postmenopausal women. There is a related high number of hospital admissions, with significant social and economic burden. Accordingly, a correct and early diagnosis of the disease is of paramount importance for public health [2-5].

The diagnosis of osteoporosis is generally made by analyzing bone mineral density (BMD) on dual-energy X-ray emission (DXA) exams [6]. Although BMD is still considered the gold standard for diagnosing osteoporosis, it is only one of the factors involved in bone strength. This can explain why individuals with normal BMD present fractures due to minimal trauma. In such cases, probably the bone quality is compromised, justifying bone fragility [7].

Several previous studies have demonstrated that changes in the cortical [8-16] and trabecular bone [16-21] of the mandible were able to identify patients with osteoporosis on panoramic radiographs, using DXA examination as the gold standard. Cone-beam computed tomography (CBCT) studies that evaluated the same bone parameters were scarce in both cortical [22-25] and mainly in trabecular bone [23,24], with controversial results for trabecular bone. However, no previous studies were found to evaluate the relationship between mandibular bone parameters in CBCT and fracture risk.

Fracture Risk Assessment Tool (FRAX) emerged as a simple alternative to assess fracture risk. This algorithm calculates individualized 10-year probability of hip and major osteoporotic fracture (lumbar spine, distal forearm, and proximal humerus). As the probability of fractures differ considerably within and across different world regions, this tool has been validated for many countries, including Brazil [26-30]. Despite FRAX still keeps its place as the most commonly used program in standard clinical practice, some authors recognize that there are some limitations for

representing bone strength. Therefore, the integration of FRAX information with advanced imaging parameters might better reflect bone fragility [31].

Some previous studies assessed the trabecular bone microarchitecture on two-dimensional (2D) and three-dimensional images (3D) [32-40]. Nevertheless, most of the bone patterns can only be observed in tridimensional images, such as micro-computed tomography (microCT) or CBCT [32,33]. These variables related to bone microarchitecture are trabecular thickness, separation and number [34,35], structure model index, trabecular pattern factor [36], degree of anisotropy [32] and fractal dimension (FD) [24].

Because CBCT is widely used in the elderly population, especially for planning dental implants, it is necessary to verify the applicability of tridimensional mandibular trabecular bone measurements to identify the population at higher risk for osteoporosis and fractures due to minimal trauma. As the vertebral region commonly appears in large field of views, it is also important to check the utility of such region for evaluating bone quality. Thus, the aim of this study was to assess tridimensional bone parameters of the second cervical vertebra and of the mandible on CBCT scans of postmenopausal women and verify whether there was a correlation between such parameters and skeletal BMD, analyzed by DXA, and fracture risk evaluated by FRAX tool.

4.2 MATERIALS AND METHODS

This observational study was performed at the University of Brasília Hospital (HUB) and approved by the Ethics Committee in Research and in accordance with the 1964 Helsinki declaration. All patients signed an informed consent. In this study, 103 patient forms were selected, of which all belonged to postmenopausal women that previously underwent DXA and CBCT exams. These forms were assessed to confirm that all had the following information: date of birth, weight, height, fracture history from both the patient and her parents, habits like alcohol intake and smoking, medication intake, and medical history regarding rheumatoid arthritis and secondary osteoporosis. It was also confirmed that the CBCTs were conducted within a maximum period of three months

from the DXA. Trabecular bone parameters were measured on 100 of the CBCT scans, due to a failure that happened when uploading 3 of the exams to the referred software. Of all these patients, only 46 had all the information registered in their patient form, enabling the application of these in the FRAX tool.

The DXA device used was the Lunar DPX NT (GE Healthcare, Madison, Wi, USA) and was operated by the same person for all the patients. BMD assessment was performed according to the World Health Organization (WHO) criteria, as follows: 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 and to better clarify bony changes in the affected and non-affected women.

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

Bone microarchitecture was evaluated using CTAn 1.10 (CT analyzer, SkyScan NV, Kontich, Belgium) by one experienced dentomaxillofacial radiologist. Two volumes of interest (VOI) were chosen to assess the trabecular bone, the first in the second cervical vertebra (VOI1) and the second anterior to the mental foramen (VOI2). The axial plane of the CBCTs was used to place both VOIs, which were subjectively set in the center of the odontoid process and between buccal and lingual cortical bones of the mandible, respectively. These VOIs were selected to avoid anatomical structure interferences and teeth, including only trabecular bone. They were shaped after a 5x5x5mm cube (Figures 1 and 2). The regions, shape and sizes were chosen in agreement to other previous studies [32-38]. The following bone parameters were evaluated: trabecular pattern factor, structure model index, trabecular thickness, trabecular number, trabecular separation, fractal dimension, and the degree of anisotropy.

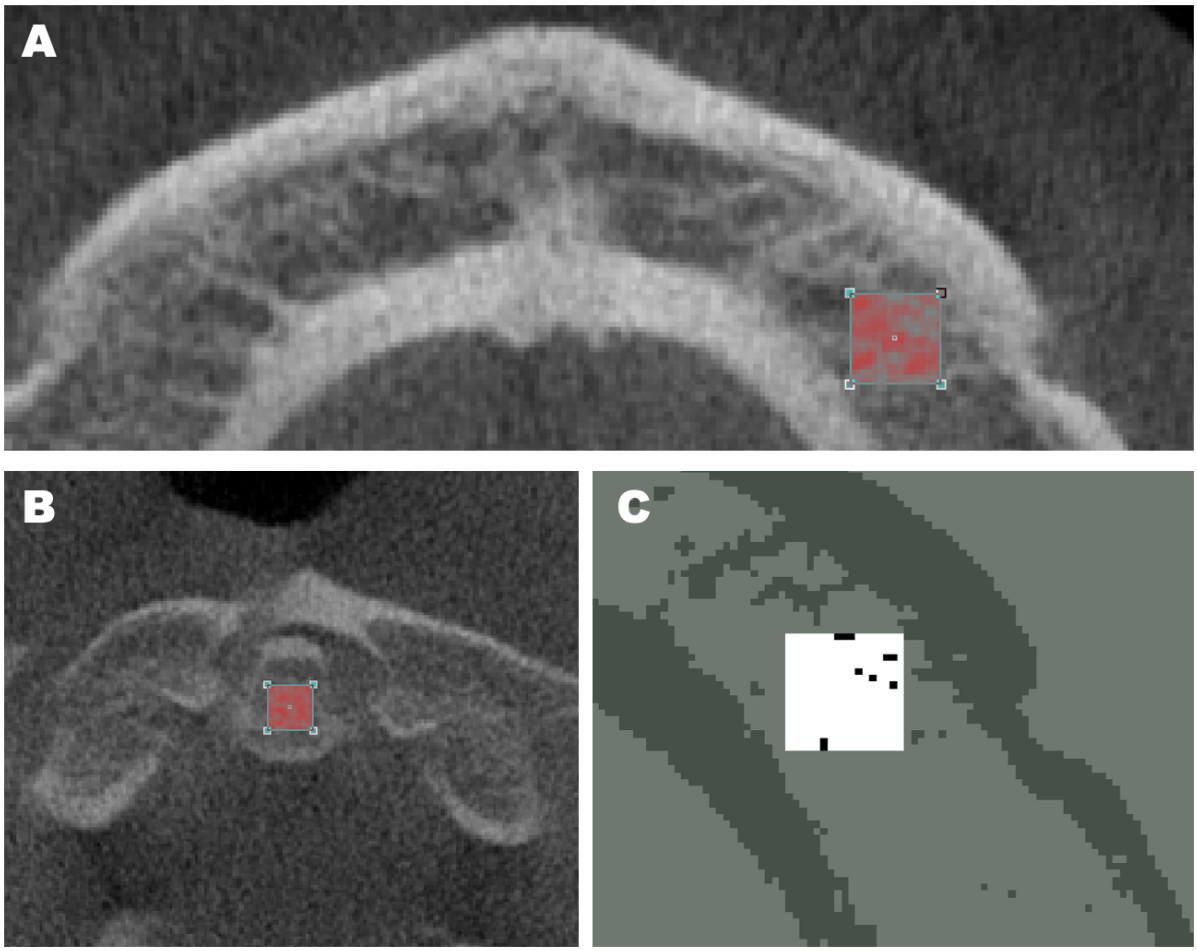

Figure 1 A – CBCT axial slice demonstrating the selection of the volume of interest 2 (5x5x5mm) on CTAn software located anteriorly to the mental foramen. B – CBCT slice demonstrating the selection of the VOI 1 (5x5x5mm) on the second cervical vertebra region C - Binary image created by CT Analyzer before analyzing the tridimensional parameters

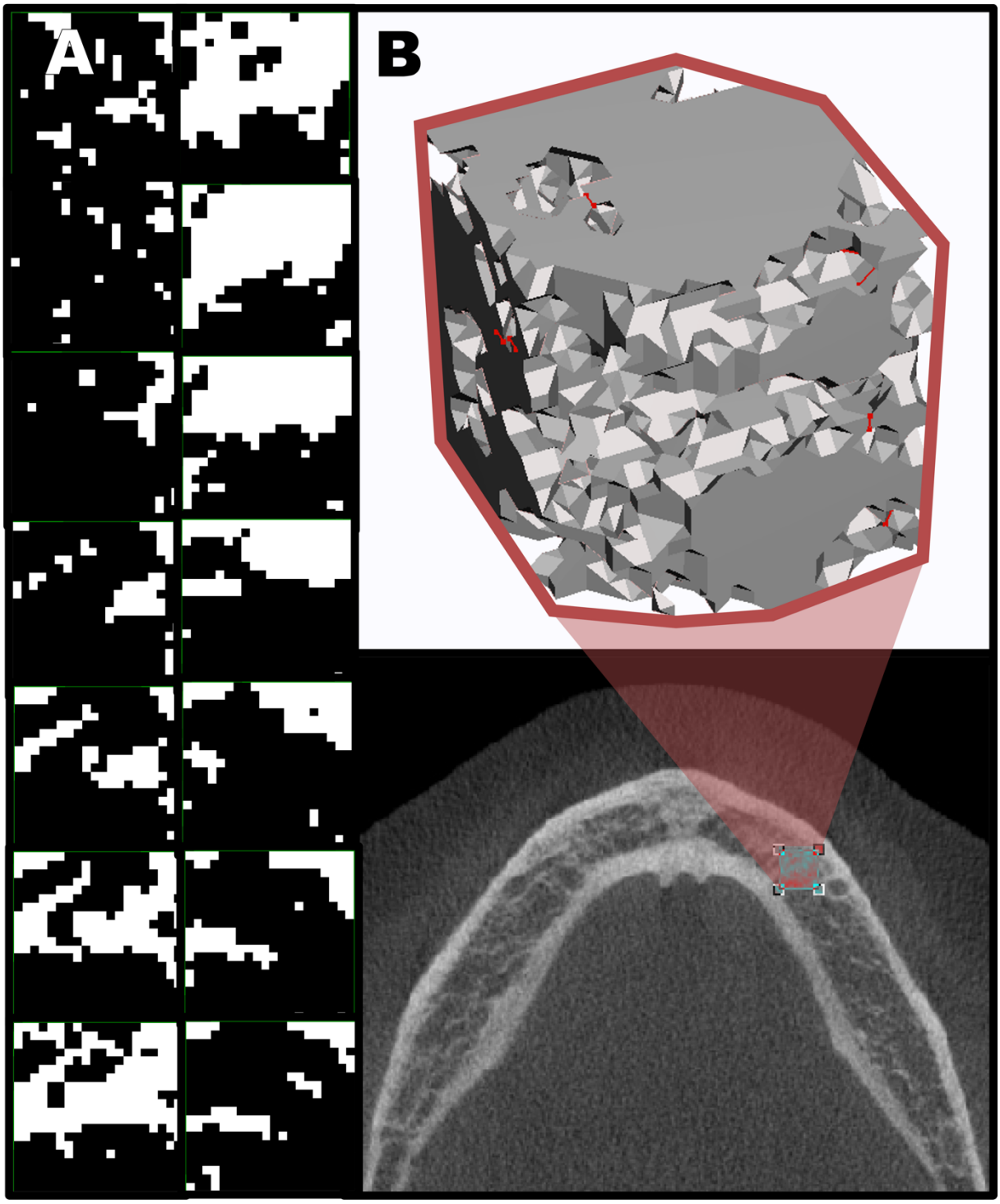

Figure 2 A – Binary images formed in the mandibular axial regions of interest to form the VOI. B – A reconstruction of the VOI formed by the various slices of the regions of interest, composed by the dataset.

FRAX tool was applied to 46 postmenopausal women from the 100 that had trabecular bone microarchitecture evaluated on the CBCT scans, following the proposed method for the Brazilian population [29,30]. 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 (Figure 3). 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 (Figure 4).

To evaluate the risk of fracture, the cut-off point proposed in the Brazilian FRAX of 3% was considered for hip fracture risk. That is, women with a high risk of hip fracture were considered as those presenting a value equal to or greater than 3% in 10 years, by the FRAX tool. For major osteoporotic fractures, the cut-off point was 15%.

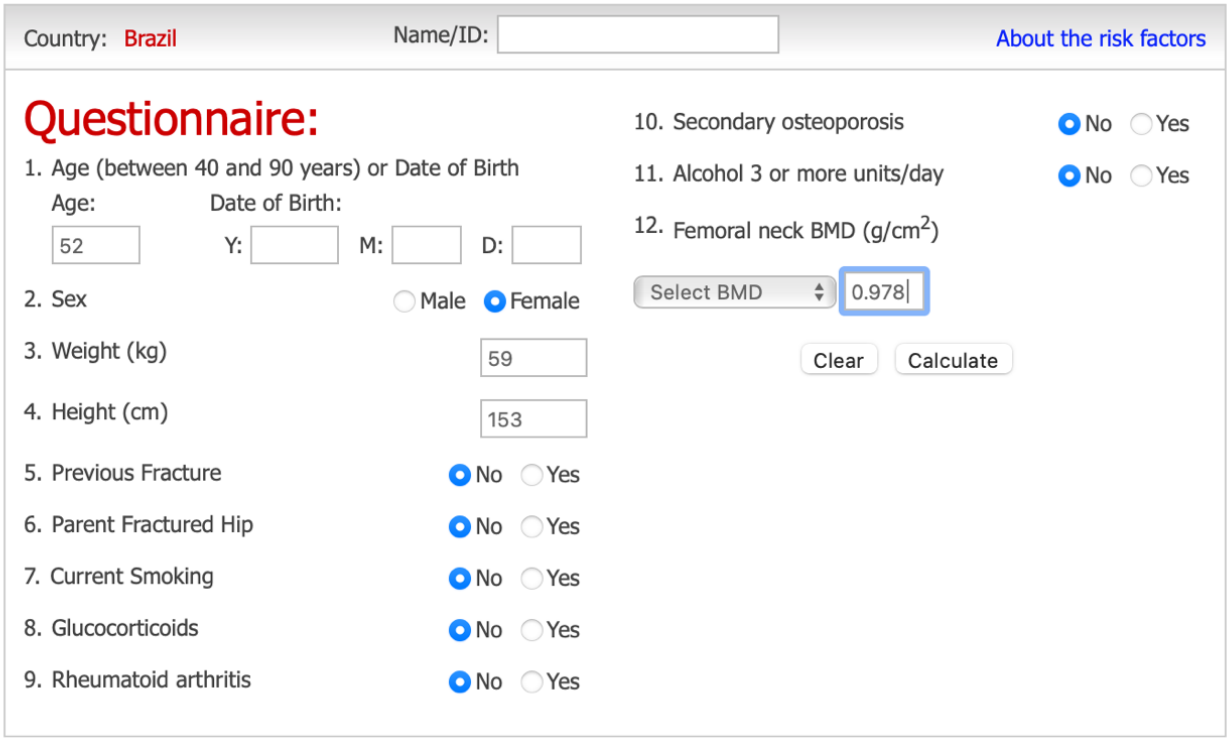

Figure 3 – Model of the FRAX questionnaire applied to the Brazilian population in order to calculate the ten-year probability of hip and major osteoporotic fractures.

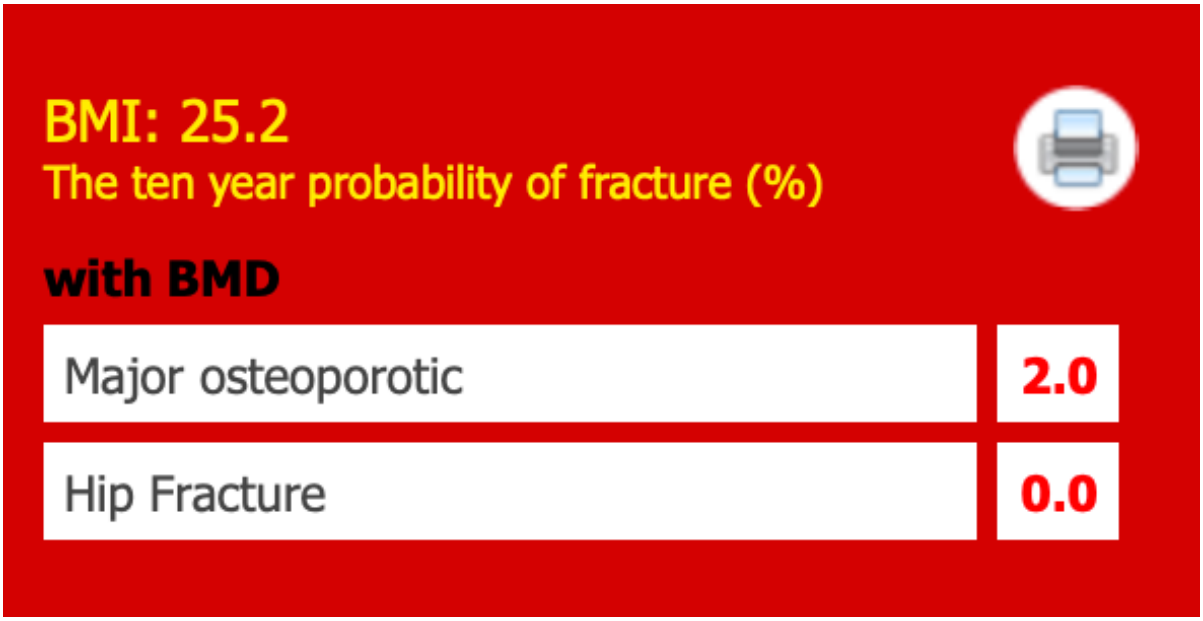

Figure 4 – Example of FRAX result. The tool shows body mass index, major osteoporotic and hip fracture risks. This example shows a 2% incidence chance of major osteoporotic fractures and 0% of hip fracture in the next 10 years.

The statistical analyses were performed with R version 4.1 (R Core Team, Vienna, Austria) [41] and Medcalc 16.8.4 (Medcalc Software bvba, Ostend, Belgium, https://medcalc.org, 2016). Chi-square test was used to verify the association between DXA and FRAX results, considering the cut-off values for low and high hip and major osteoporotic fracture risks. Spearman correlation coefficients were used to test the correlations among all bone parameters, skeletal BMD and FRAX results. Afterwards, a linear regression model was created using the significant variables. A stepwise multiple linear regression model was used to compare the most significant results. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off threshold of the bone parameters for identifying low and high fracture risk according to FRAX cut-off values. Differences in CBCT cortical and trabecular measurement values between two FRAX-based fracture risk groups (<3% and ≥3%) were analysed using the non-parametric Mann-Whitney test. P values of <.05 were considered to be statistically significant for all statistical tests.

4.3 RESULTS

The 100 study patients were postmenopausal women with a mean age 63.9 (± 9.7 years). All vertebral bone parameters (VOI1) correlated with BMD at the three bone sites, except trabecular pattern factor and fractal dimension (Table 1). Regarding mandibular bone parameters (VOI2), only trabecular number and thickness parameters correlated with skeletal BMD (Table 2).

Table 1 – Correlations between trabecular bone parameters measured at the vertebral volume of interest (VOI1) and skeletal BMD at the three bone sites (lumbar spine, femoral neck and total hip)

Vertebral bone parameters	**BMD lumbar spine**	**BMD femoral neck**	**BMD total hip**
Trabecular bone pattern	-0.150	-0.152	-0.190
Structure model index	-0.263	-0.260	-0.297
Trabecular thickness	-0.536	-0.499	-0.499
Trabecular number	0.476	0.504	0.509
Trabecular separation	0.292	0.233	0.225
Fractal dimension	0.082	-0.041	-0.014
Degree of anisotropy	-0.493	-0.416	-0.411

The variables highlighted in gray presented statistically significant correlations ($p<0.05$)

Table 2 – Correlations between trabecular bone parameters measured at the mandibular volume of interest (VOI2) and skeletal BMD at the three bone sites (lumbar spine, femoral neck and total hip)

Mandibular bone parameters	**BMD lumbar spine**	**BMD femoral neck**	**BMD total hip**
Trabecular bone pattern	0.028	-0.027	-0.001
Structure model index	-0.117	-0.147	-0.138
Trabecular thickness	-0.251	-0.219	-0.244
Trabecular number	0.305	0.298	0.288
Trabecular separation	0.014	-0.012	0.047
Fractal dimension	0.004	0.007	-0.006
Degree of anisotropy	-0.091	-0.123	-0.132

The variables highlighted in gray presented statistically significant correlations ($p<0.05$)

From the total sample, FRAX tool was applied to 46 postmenopausal women with a mean age 63.2 (± 9.5 years). From these women, 13 (28.3%) postmenopausal women 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%. Table 3 shows the distribution of all studied women according to DXA and FRAX cut-off values. There was an association between DXA and FRAX results only for hip fracture risk. When comparing the variables obtained from FRAX (hip fracture risk and major fracture risk) with the vertebral bone measurements significant correlations were found for the trabecular thickness, trabecular number, and the degree of anisotropy (Table 4). Trabecular number was also relevant in the evaluation of the mandibular VOI (Table 5).

Table 3 – 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 4 – Correlations between trabecular bone parameters measured at the vertebral volume of interest (VOI1) and FRAX results

Vertebral bone parameters	**Hip Fracture risk**	**Major Fracture risk**
Trabecular bone pattern	-0.030	0.030
Structure model index	0.100	0.110
Trabecular thickness	0.360	0.340
Trabecular number	-0.350	-0.360
Trabecular separation	-0.016	-0.100
Fractal dimension	-0.020	-0.003
Degree of anisotropy	0.390	0.350

The variables highlighted in gray presented statistically significant correlations ($p<0.05$)

Table 5 – Correlations between trabecular bone parameters measured at the mandibular volume of interest (VOI2) and FRAX results

Mandibular bone parameters	Hip Fracture risk	Major Fracture risk
Trabecular bone pattern	0.120	-0.120
Structure model index	0.300	0.250
Trabecular thickness	0.180	0.090
Trabecular number	-0.400	-0.360
Trabecular separation	0.027	0.026
Fractal dimension	0.0160	0.016
Degree of anisotropy	0.182	0.150

The variables highlighted in gray presented statistically significant correlations ($p<0.05$)

According to the linear regression model (table 6), the trabecular number assessed in the mandible showed the most promising results in comparison to the other variables, since it presented a strong inverse correlation both for hip fractures and major osteoporotic fractures. Moreover, trabecular number parameter was significantly lower in the lowest hip fracture risk group (Median 0.31) compared to the highest risk group (Median 0.38), $p = 0.01$. Considering this result, a ROC curve analysis was performed for the trabecular number parameter (Figure 4).

An area under the curve (AUC) of 0.732 for trabecular number to identify high hip fracture risk based on FRAX was found. Based on this *ROC* curve analysis (Youden index J), the cut-off value for the trabecular number at the mandible (VOI2) was 0.32. Below this value, the following accuracy measurements were: 69.2% sensitivity, 82% specificity, 3.8 positive likelihood ratio, 0.38 negative likelihood ratio.

Table 6 – Univariate and multivariate regression models using FRAX results, trabecular bone parameters, age and body mass index.

Variables	**Univariate**			**Multivariate**		
Hip Fracture Risk	**Beta**	**95% LL**	**95% UL**	**Beta**	**95% LL**	**95% UL**
Trabecular thickness (VOI1)	0.956	0.210	1.702	-	-	-
Trabecular number (VOI1)	-6.507	-11.75	-1.255	-	-	-
Degree of anisotropy (VOI1)	2.610	0.718	4.502	-	-	-
Structure model index (VOI2)	0.761	0.023	2.499	-	-	-
Trabecular number (VOI2)	-9.994	-16.92	-3.058	-6.113	-11.708	-0.518
Age	0.028	-0.056	0.112	0.053	-0.006	0.113
Body mass index	-0.280	-0.410	-0.151	-0.212	-0.325	-0.099
Major fracture risk						
Trabecular thickness (VOI1)	1.503	0.259	2.746	-	-	-
Trabecular number (VOI1)	-11.11	-19.76	-2.465	-	-	-
Degree of anisotropy (VOI1)	3.965	0.791	7.138	-	-	-
Trabecular number (VOI2)	-14.97	-26.65	-3.304	-9.662	-20.08	0.757
Age	0.042	-0.097	0.181	0.082	-0.029	0.194
Body mass index	-0.424	-0.646	-0.202	-0.332	-0.543	-0.121

LL = Lower limit, UL = upper limit. VOI1 = volume of interest at the vertebral site. VOI2 = volume of interest at the mandible. The variable highlighted in gray presented the most significant results.

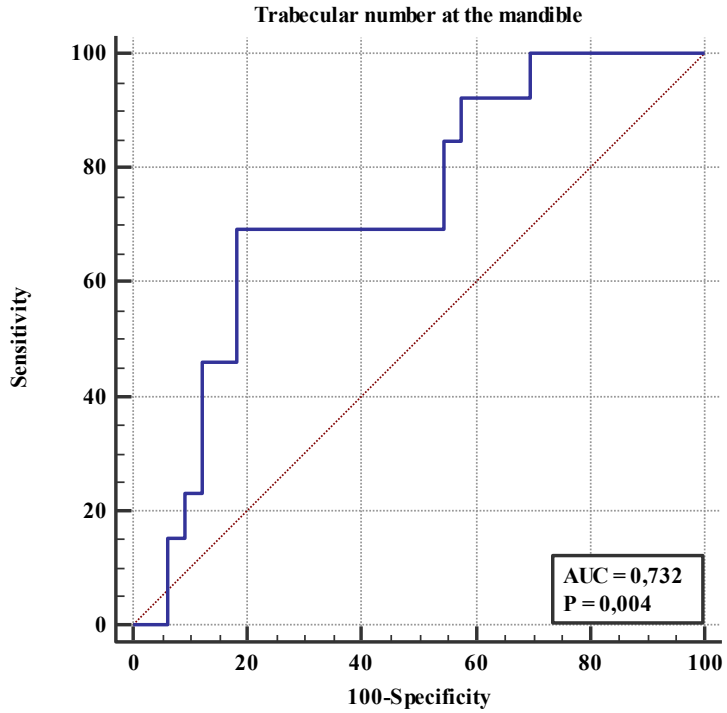

Figure 4 – ROC curve analysis for identifying postmenopausal women with hip fracture risk ≥ 3%

4.5 PRELIMINARY DISCUSSION

This study analyzed several trabecular bone parameters on CBCT scans of 100 postmenopausal women, with a widely used software in microCT analyses. Two volumes of interest (VOI) at the mandible and second cervical vertebra were selected on the images in order to calculate the parameters related to bone microarchitecture. Significant relationships were found among these parameters and skeletal BMD. There was a significant association between DXA and FRAX results. Moreover, trabecular number measured at the mandibular VOI demonstrated significant negative correlation with a higher risk of hip fracture based on FRAX. This pioneer study demonstrated that CBCT parameters can be used to screen postmenopausal women with bone strength reduction considering not only low BMD, but also bone fragility.

The study design was based on the fact that the screening of patients with the disease and mainly with higher risk for fracture is crucial for the health system. Osteoporosis fracture is a serious problem affecting aging population worldwide. Its complications may lead to the risk of mobility reduction, increased cost of care, and morbidity [42]. Thus, the identification of microstructural bone alterations in dental exams of common use in clinical practice could serve as an auxiliary tool for early

identification of the highest fracture risk group. We hypothesized that CBCT images enable an accurate identification of trabecular bone microarchitecture and therefore would be able to screen postmenopausal women with low BMD and high fracture risk.

Although microCT is considered the gold standard in evaluating trabecular bone structure, its usage is limited to *ex vivo* analyses, hence, it cannot be used to evaluate bone microarchitecture in patients. For *in vivo* studies, high-resolution peripheral computed tomography (HR-pQCT) is considered the best technique to measure the bone microarchitecture, but its design allows to scan only extremities such as distal radius and tibia [43]. Therefore, CBCT may overcome some of the limitations. On the other hand, this method has also its inherent limitations, such as artefacts that may hamper image quality and consequently any image-based quantitative evaluation. Three previous *ex vivo* studies with bone biopsies, had previously demonstrated a high correlation amongst bone parameters measured on CBCT and microCT, such as trabecular thickness, number, and separation [34, 37, 43].

In spite of the fact that some previous studies have already assessed the trabecular bone microarchitecture on two-dimensional (2D) and three-dimensional images (3D) [32-40], to the best of the author's knowledge this is the first study to demonstrate significant correlations between such parameters and both BMD and FRAX results.

Some authors mention FRAX to be the fracture predicting tool which is most used globally. The reason for this may be related to its flexibility regarding patients who have and who do not have the DXA data such as DMO or T-Score. The tool is also advantageous due to its country specificity [45]. We found FRAX a very innovative tool, since studies comparing its results with trabecular bone microarchitecture are very scarce. Its results may also lead to predominant treatment decisions, for example when indicating osteoporosis medication. When the patients present a T-Score between -2.5 and -1 (osteopenia) and a major osteoporotic fracture chance of 20% or over and hip fracture of 3% or over, they are recommended to undergo a medication-based osteoporosis approach [46].

This study's limitations can be found when assessing the number of women who participated in the study with the information for the FRAX tool. Many of them were not included, in view of the fact that some unique information was either missing from their file, or they did not want to answer the form, like alcohol intake. Another limitation can be found related to the exams being done in the same CBCT device, with no voxel

comparisons or any combinations of tube parameters, as shown by some other studies [38].

This study's samples were CBCT images with 0.25mm voxel size. Other studies showed that there are great differences when comparing images created by an i-Cat device, like the one used in the present study and images from an Accuitomo device at 0.125mm [44], for example. Although some other authors already demonstrated the possibility to use 0.25mm voxel CBCTs to screen osteoporosis with the use of conventional software [40]. In spite of the fact that this could be considered a limitation, the present study meant to assess trabecular bone parameters in a common CBCT device, to help find out whether it is feasible to conduct such an assessment on a daily basis.

In conclusion, much has been found and learned by this study regarding bone microarchitecture and its correlation to BMD and fracture risk. The FRAX tool is a very clean fracture risk questionnaire, of which the data can be easily included in the anamneses. Tomography devices like CBCT are not hard to find in Brazil, making it viable to use as an adjuvant tool to calculate the risk of fragility fractures or even to indicate patients to a rheumatologist through their bone parameters. Since trabecular number showed such promising results, it is suitable to indicate and continue further research to enlighten the clinical applications of this study.

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CAPÍTULO 5 - DISCUSSÃO GERAL E CONCLUSÕES DA TESE

Esta 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 1, capítulo 2 [1]. Por outro lado, a análise da dimensão fractal não demonstrou boa acurácia e reprodutibilidade para predizer a osteoporose identificada pela densitometria, conforme evidenciado no artigo 2, capítulo 3 [2]. Já os parâmetros trabeculares, avaliados de forma tridimensional, como o número e a espessura das trabéculas e anisotropia apresentaram correlação com os resultados do FRAX, com potencial para predizer o risco de fratura, conforme demonstrado no artigo 3, capítulo 4 da tese.

O artigo 1 foi o primeiro estudo de teste diagnóstico que analisou a acurácia e reprodutibilidade dos índices qualitativos e quantitativos em TCFC para identificar pacientes com baixo índice de DMO, e apresenta um modelo preditivo para identificar pacientes osteoporóticos com base nas medidas de TCFC e na idade, 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 em duas imagens de reconstrução de TCFC diferentes (panorâmicas e transversais). 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 cortical e 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 pós-menopausa que foram submetidas a exames de TCFC para fins odontológicos [1].

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 [3]. Para esta avaliação, os autores encontraram valores de acurácia

inferiores aos encontrados no presente estudo, com área sob a curva ROC de 0,576 e fizeram as avaliações em reconstruções panorâmicas com diferentes espessuras. No presente estudo, 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 oblíquas. 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, com área sob a curva de 0,8 [1].

No entanto, este modelo necessita ser testado em outras populações. Além disso, a avaliação da TCFC pelo radiologista e o relatório deste exame precisam 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 osseointegrados.

O artigo 2 [2], capítulo 3 da tese, avaliou o parâmetro ósseo trabecular dimensão fractal na TCFC, utilizando a mesma amostra de mulheres na pós-menopausa do artigo 1 [1]. Os valores médios de dimensão fractal foram significativamente menores na região mandibular de interesse dos pacientes osteoporóticos quando comparados a indivíduos 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 compararam as análises de dimensão fractal na mandíbula com dados do exame de DXA [4,5], 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. Uma pequena região de interesse foi selecionada em imagens coronais de TCFC e não houve diferença significativa na análise entre os dois grupos. Güngör et al (2016) também avaliaram a DF, porém em sítios distintos aos dos demais estudos (na cabeça da mandíbula, na maxila e na cortical mandibular) e com uma metodologia de cálculo de DF diferente do método clássico preconizado por White & Rudolph em 1999 [6]. Somente a região de interesse localizada no lado esquerdo da maxila mostrou resultados significativamente menores em indivíduos osteoporóticos do que no grupo de controle.

Ainda com distintas abordagens metodológicas, os três estudos prévios que analisaram DF em TCFC apontam no mesmo sentido, ou seja, que esta análise é ainda limitada para ser utilizada como ferramenta auxiliar no rastreamento de pacientes com osteoporose. A identificação de alterações trabeculares seria fundamental, visto que o osso trabecular é mais sensível às alterações da doença e possui um metabolismo oito vezes maior que o osso cortical. Além disso, o osso trabecular parece indicar mais a qualidade óssea, que representa cerca de 50% da resistência óssea, sendo os outros 50% representados pela DMO. Nesse sentido, este parâmetro poderia justificar a ocorrência de fraturas por trauma mínimo em indivíduos com a DMO normal [7-10]. Todavia, o presente estudo demonstrou que, apesar de diferenças na DF 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 trabalho 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.

Para suprir a limitação supracitada do artigo 2, o artigo 3 procurou analisar parâmetros ósseos trabeculares tridimensionalmente, com o auxílio de um programa muito utilizado em MicroCT. Por meio da seleção de um volume de interesse (VOI), diversos parâmetros trabeculares foram calculados e feita a correlação com o algoritmo FRAX, que analisa o risco de fratura baseado em fatores de risco clínicos.

O delineamento deste último estudo se baseou no fato que, mais que o diagnóstico precoce da doença, deve-se buscar o rastreamento dos pacientes com maior risco para fratura. A identificação de alterações ósseas microestruturais em exames odontológicos de uso corriqueiro na prática clínica poderia servir como ferramenta auxiliar para esta finalidade.

A escolha da ferramenta para análise do risco de fratura foi baseada em sua ampla aplicabilidade no mundo e sua validação nos diversos países, incluindo o Brasil [13-17]. A ferramenta FRAX é de simples aplicação e pode ser feita por qualquer profissional de saúde treinado, incluindo o cirurgião-dentista.

As variáveis definidas como mais promissoras pela atual pesquisa foram o número trabecular, a espessura trabecular e a anisotropia, segundo os modelos de regressão, principalmente o número de trabéculas. Estas três variáveis apresentaram boa correlação com o risco de fratura calculado pela FRAX tanto para fratura de

quadril, como para fraturas osteoporóticas maiores, quando analisadas no volume de interesse (VOI) da segunda vértebra cervical. O VOI anterior ao forame mentual teve boa correlação com o número trabecular e o resultado da ferramenta FRAX, sendo uma região de fácil acesso aos exames realizados no dia a dia, devido à inclusão desta região na maioria dos exames.

No entanto, ainda se faz necessário verificar se estes parâmetros ósseos trabeculares tridimensionais têm acurácia para predizer o risco de fratura. Além disso, como limitação do último artigo, a coleta dos dados do FRAX somente foi possível em um número mais reduzido de 46 mulheres. Logo, estes parâmetros devem ser testados quanto à acurácia, reprodutibilidade e em outros grupos populacionais, incluindo a população masculina. Deve-se ressaltar que a osteoporose em homens idosos, acima de 60 anos, é considerada como um problema de saúde pública mundial, ainda que a atenção esteja mais voltada para as mulheres na pós-menopausa, que representam o principal grupo de risco para a doença. Em homens idosos, o risco de mortalidade por uma fratura de quadril por osteoporose, em razão das comorbidades, é duas vezes maior que nas mulheres [16,17].

Portanto, ainda existe o desafio de incluir o cirurgião-dentista e, mais especificamente, o radiologista que analisa os exames de imagem odontológicos para que ele incorpore na sua rotina de avaliação e, consequentemente, na sua prática profissional, a identificação de alterações ósseas corticais e trabeculares que sugiram uma baixa DMO e um risco aumentado para fraturas por trauma mínimo. O envelhecimento da população mundial reforça ainda mais a necessidade de uma mudança de paradigma na prática odontológica, com o aumento significativo da osteoporose e das fraturas relacionadas [17]. As demais doenças crônicas também aumentarão e há necessidade de identificação precoce de diagnosticá-las precocemente pelos profissionais de saúde. A própria mudança de currículo no ensino da Odontologia se faz necessária com a mudança do perfil epidemiológico [18].

Ainda que o cirurgião-dentista possa não estar devidamente treinado ou instruído a identificar indivíduos com baixa DMO e osteoporose e exames de imagem odontológico, a automação de processos por meio de algoritmos de inteligência artificial poderá servir como uma “terceira visão” ao profissional que analisa a imagem, auxiliando na detecção e classificação de doenças [19]. Já existem estudos preliminares bastante promissores que desenvolveram algoritmos de aprendizado de

máquinas (*machine learning*) capazes de identificar mulheres com osteoporose em radiografias panorâmicas [20-23].

Nos últimos anos, houve uma rápida expansão no desenvolvimento e uso de tecnologias digitais. Inspirados pelos processos de funcionamento do cérebro humano, em particular a adaptação para resolver problemas não lineares e para descobrir tendências sutis e associações entre variáveis, as ferramentas de inteligência artificial são algoritmos computacionais que foram desenvolvidos para desenvolvimento de tarefas antes restrita à inteligência humana. A inteligência artificial provou ser valiosa para compreender e ligar as relações entre as variáveis de sistemas complexos como os relatados na osteoporose multifatorial [24]. Tanto a aprendizagem de máquinas quanto modelos de aprendizagem profunda possuem aplicações na osteoporose. Vários estudos foram publicados com o objetivo de prever um indicador de osteoporose, como DMO ou fraturas, ou como uma ferramenta para segmentação automática das imagens de pacientes com ou em risco de osteoporose. Exemplos são aquelas ferramentas que utilizaram estes algoritmos para prever o resultado de DMO [25, 26] ou para predizer a classificação de pacientes com fraturas/não fraturas [27-29] e diagnóstico da doença [30]

O uso de ferramentas de avaliação de fraturas por trauma mínimo é imperativo no cuidado do idoso e um desafio importante no enfrentamento da osteoporose, o FRAX ainda mantém seu lugar como o meio mais eficiente e disponível na prática clínica [13-17]. Ao identificar quais pacientes se beneficiariam mais com o exame ou tratamento com DXA, as ferramentas de avaliação de risco podem contribuir para a tomada de decisões na área de saúde. Alternativamente, um algoritmo mais sofisticado integrando não apenas múltiplos fatores de risco como variáveis FRAX, mas também parâmetros avançados de imagem, medidas de desempenho físico e dados genéticos podem ser desenvolvidos [24]. Embora ainda em desenvolvimento, estas ferramentas de inteligência artificial certamente se constituirão em grandes mecanismos de auxílio no diagnóstico, na prevenção e no acompanhamento dos pacientes com este grave problema de saúde pública no mundo todo.

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5.2 CONCLUSÕES

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 de 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 mandibular e também na segunda vértebra cervical não apresentou acurácia e boa reprodutibilidade para predizer o diagnóstico densitométrico de osteoporose.

Nos exames de TCFC, houve correlação de parâmetros ósseos trabeculares tridimensionais analisados tanto na segunda vértebra cervical como na mandíbula (o mais promissor sendo o número de trabéculas), com o risco de fratura avaliado pela ferramenta FRAX e os valores de densidade mineral óssea. Isso indica a possibilidade de aplicar na prática clínica e no dia a dia dos cirurgiões dentistas estas análises tridimensionais, possibilitando assim o diagnóstico precoce da doença através de indicações à reumatologia quando necessário. O estudo também demonstrou que os exames de TCFC podem ter um impacto socioeconômico positivo ao identificar paciente com alto risco de fraturas por fragilidade óssea.

CAPÍTULO 6 - PRESS RELEASE

Durante toda a vida o ser humano é submetido à realização de alguns exames para o diagnóstico de alguma doença ou até mesmo o planejamento de algum procedimento. Para os procedimentos odontológicos não é diferente. Sendo assim, as tomografias computadorizadas de feixe cônico estão cada vez mais presente nas indicações de tratamentos odontológicos e também possibilitam algumas avaliações, além das previstas pelo profissional que as indica. Esta pesquisa teve como objetivo pesquisar se é possível avaliar alguns aspectos do osso da mandíbula e saber se estes podem ou não ajudar a estabelecer riscos de fraturas atraumáticas. Com isso, foram avaliadas 103 tomografias de mulheres na pós-menopausa avaliando estes aspectos ósseos e comparando-os com os dados do exame de densitometria óssea e com o risco de fratura calculado por uma ferramenta validada pela literatura chamada FRAX. Os resultados demonstram que existe uma relação entre o afilamento da cortical da mandíbula e sua reabsorção com a presença da osteoporose. Além disso, alguns parâmetros no osso mandibular têm relação com o risco de fratura por osteoporose. A metodologia aplicada pelo estudo tem caráter promissor para rastreamento de pessoas com a doença e com risco de fratura. Essa avaliação precoce pelo cirurgião-dentista poderá auxiliar na redução do impacto socioeconômico causado pela doença, ajudando a melhorar também a qualidade de vida das pessoas.

APÊNDICE

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ORIGINAL ARTICLE

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

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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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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

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ANEXO

DADOS DA VERSÃO DO PROJETO DE PESQUISA

Título da Pesquisa: Dimensão fractal do trabeculado ósseo mandibular em mulheres na pós-menopausa e homens acima de 60 anos com e sem osteoporose.
Pesquisador Responsável: Bruno Fontenele Carvalho
Área Temática:
Versão: 4
CAAE: 47725915.1.0000.0030
Submetido em: 02/11/2015
Instituição Proponente: FACULDADE DE SAÚDE - FS
Situação da Versão do Projeto: Aprovado
Localização atual da Versão do Projeto: Pesquisador Responsável
Patrocinador Principal: Financiamento Próprio

Comprovante de Recepção: PB_COMPROVANTE_RECEPCAO_487335