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**Incidência e fatores de risco para fratura vertebral por
osteoporose em idosos brasileiros da comunidade:
um estudo prospectivo de base populacional.
*São Paulo Ageing & Health (SPAH) Study***

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Universidade de São Paulo para obtenção do título
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Orientadora: Prof^ª. Dr^ª. Rosa Maria Rodrigues Pereira

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LISTA DE ABREVIATURAS E SIGLAS

25OHD	- 25-hidroxivitamina D
CTX	- Telopeptídeo-C do colágeno tipo I
DMO	- Densidade mineral óssea
DXA	- <i>Dual X-ray Absorptiometry</i>
IBGE	- Instituto Brasileiro de Geografia e Estatística
IMC	- Índice de massa corporal
MVS	- Mínima variações significativa
P1NP	- Propeptídeo N-terminal do colágeno tipo I
PRO-AIM	- Programa de Aprimoramento das Informações de Mortalidade
PTH	- Hormônio da paratireoide
RR	- Risco relativo
SPAH	- <i>São Paulo Ageing & Health</i>
SQ	- Semiquantitativo
TFG	- Taxa de filtração glomerular

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RESUMO

Domiciano DS. *Incidência e fatores de risco para fratura vertebral por osteoporose em idosos brasileiros da comunidade: um estudo prospectivo de base populacional. São Paulo Ageing & Health (SPA) Study*. [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2014.

As fraturas vertebrais por osteoporose conferem risco aumentado de novas fraturas por fragilidade e maior mortalidade. Não há dados consistentes acerca da incidência de fraturas vertebrais osteoporóticas em países de baixa e média rendas que têm experimentado aumento da expectativa de vida e envelhecimento populacional acelerado nas últimas décadas. Os objetivos deste estudo foram: determinar a incidência de fraturas vertebrais osteoporóticas diagnosticadas por radiografia e identificar os principais fatores de risco para fratura em idosos brasileiros da comunidade, em um estudo coorte prospectivo de base populacional. Setecentos e sete indivíduos da comunidade (com mais de 65 anos) foram avaliados através de radiografias da coluna vertebral obtidas no início do estudo e após um tempo médio de seguimento de $4,3 \pm 0,8$ anos. Fratura nova ou incidente foi definida como uma alteração na morfologia vertebral, resultando em maior grau de deformidade na segunda radiografia (graus 1-3) quando comparado ao exame inicial. Na avaliação inicial, realizaram-se questionário (dados clínicos), a medida da densidade mineral óssea (DMO) e exames laboratoriais. Modelos de regressão multivariada de Poisson foram construídos para identificar os preditores independentes de fratura vertebral. Quatrocentos e quarenta e nove mulheres ($72,9 \pm 4,8$ anos) e 258 homens ($72,3 \pm 4,7$ anos) foram incluídos no estudo. A incidência de fratura vertebral ajustada para a idade foi de 40,3/1000 pessoas/ano em mulheres e 30,6/1000 pessoas/ano em homens. Na análise multivariada, foram determinados três possíveis modelos de fatores de risco para fratura em mulheres: a) idade (RR 2,46, IC 95% 1,66-3,65 para cada aumento em 10 anos), fratura osteoporótica prévia (RR 1,65, IC 95% 1,00-2,71) e DMO da coluna lombar (RR 1,21, IC 95% 1,03-1,41 para cada redução de 1 DP na DMO); b) idade (RR 2,25, IC 95% 1,52-3,34 para cada aumento em 10 anos) e DMO do colo do fêmur (RR 1,42, IC 95% 1,11-1,81 para cada redução de 1 DP na DMO); c) idade (RR 2,11, IC 95% 1,41-3,15 para cada aumento em 10 anos) e DMO do quadril total (RR 1,56, IC 95% 1,21-2,0 para cada redução de 1 DP na DMO). Em homens, o maior quartil de distribuição do telopeptídeo C-terminal do colágeno tipo I (CTX) (RR 1,96, IC 95% 0,98-3,91) e fratura prévia (RR 2,10, 95% CI 1,00-4,39)

foram preditores de nova fratura vertebral após ajustes para idade, peso e atividade física. Este é o primeiro estudo longitudinal que determinou a incidência de fraturas vertebrais em uma amostra de base populacional de idosos na América Latina. A frequência de fraturas vertebrais foi elevada nessa população. Idade, fratura prévia, DMO e marcadores bioquímicos da remodelação óssea foram preditores de nova fratura vertebral.

Descritores: Fraturas da coluna vertebral. Idoso. Osteoporose. Incidência. Fatores de risco. Epidemiologia. Radiografia. Coluna vertebral.

SUMMARY

Domiciano DS. *Incidence and risk factors for osteoporotic vertebral fracture in Brazilian community-dwelling elderly: a population-based prospective study. The São Paulo Ageing & Health (SPAH) Study*. [thesis]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2014.

Vertebral fractures are associated with increased future fracture risk and mortality. No data on incidence of osteoporotic vertebral fracture have been reported in low-income countries where the population's aging has been faster. Thus, we sought to describe the incidence and risk factors for radiographic vertebral fracture in a longitudinal prospective Brazilian population-based elderly cohort. 707 older adults (449 women and 258 men) were evaluated with spinal radiographs obtained at baseline and after a mean follow-up of 4.3 ± 0.8 years. New vertebral fracture was defined as distinct alteration in the morphology of vertebrae resulting in higher grade of deformity on the second radiograph when compared to the baseline radiograph. Clinical questionnaire, bone mineral density (BMD), and laboratory tests were performed at baseline. Multivariate Poisson regression models were used to identify independent predictors of fracture. The age-standardized incidence of vertebral fracture was 40.3/1,000 person-years in women and 30.6/1,000 in men. In women, three models of risk factors for fracture were fitted: (a) age (relative risks (RR) 2.46, 95 % confidence interval (CI) 1.66-3.65), previous osteoporotic fracture (RR 1.65, 95 % CI 1.00-2.71), and lumbar spine BMD (RR 1.21, 95 % CI 1.03-1.41); (b) age (RR 2.25, 95 % CI 1.52-3.34) and femoral neck BMD (RR 1.42, 95 % CI 1.11-1.81); (c) age (RR 2.11, 95 % CI 1.41-3.15) and total hip BMD (RR 1.56, 95 % CI 1.21-2.0). In men, the highest quartile of cross-linked C-telopeptide (CTX) (RR 1.96, 95 % CI 0.98-3.91) and prior fracture (RR 2.10, 95 % CI 1.00-4.39) were predictors of new vertebral fracture. This is the first population-based study to ascertain the incidence of vertebral fracture in elderly Latin Americans, confirming the high frequency of the disorder. Age, prior fracture, BMD, and bone turnover were predictors of the short-term incidence of vertebral fracture.

Descriptors: Spinal Fractures. Aged. Osteoporosis. Incidence. Risk factors. Epidemiology. Radiography. Spine.

1 INTRODUÇÃO

O envelhecimento populacional é um fenômeno mundial, porém mais acelerado em países subdesenvolvidos¹. Atualmente, 65% dos idosos residem em países menos desenvolvidos e a expectativa é que esse valor atinja quase 80% em 2050². O Brasil é um país de baixa e média rendas que passa por uma intensa transição sociodemográfica, com um dos mais acelerados ritmos de envelhecimento populacional do mundo³. Hoje, pessoas com idade de 60 anos ou mais compõem 13,0% da população brasileira, mas espera-se que esse grupo represente quase 20% de toda a população em 2030⁴. A expectativa de vida para os nascidos entre 1950 e 1955 era de 51 anos; as estimativas para os nascidos entre 2000 e 2005 aumentaram para 74 anos².

A população adulta brasileira experimentou mudanças socioeconômicas marcantes que rapidamente transformaram um país essencialmente rural em uma sociedade urbana diversificada^{1,3}. Muitos idosos que nasceram em áreas rurais agora vivem em centros urbanos e representam aqueles que sobreviveram às elevadas taxas de mortalidade infantil, suportando adversidades socioeconômicas significativas, como nenhuma ou pouca educação escolar e ocupações não qualificadas e mal remuneradas na idade adulta⁵. A atual transição demográfica faz parte de um processo mundial que vem ocorrendo em países de baixa e média rendas na América Latina, África e Ásia¹.

Com o envelhecimento da população e o aumento da expectativa de vida, espera-se considerável incremento nos gastos com doenças crônicas (como a

osteoporose) em países de baixa renda. Portanto, o conhecimento sobre a incidência e os fatores de risco para fraturas osteoporóticas adquire especial importância para as políticas de saúde pública nessas populações. Além disso, nota-se um crescimento no número de idosos do sexo feminino: no Brasil, por exemplo, as mulheres representam 55,5% da população idosa e 61% do número de indivíduos idosos com mais de 80 anos. Grande parcela dessa população feminina tem baixo nível socioeconômico⁶ e representa, portanto, os maiores dependentes dos cuidados de saúde. A constatação de tal fato reforça a preocupação com a frequência de fraturas por osteoporose em populações de baixa renda, uma vez que elas são mais comuns em indivíduos do sexo feminino. A fratura osteoporótica mais frequente é a fratura vertebral^{17,8}, que afeta cerca de 20% das mulheres na pós-menopausa⁷.

Apenas 25-30% das fraturas vertebrais são sintomáticas e chegam à atenção médica⁸. Portanto a imagem radiológica da coluna deve ser solicitada para qualquer indivíduo com baixa massa óssea ou que apresente fatores clínicos de risco para fratura por fragilidade⁹. Apesar disso, o subdiagnóstico de fraturas vertebrais é muito frequente na prática clínica¹⁰⁻¹². No estudo IMPACT, as taxas de falso-negativos variaram entre 29,5% e 46,5% em laudos radiológicos, apesar de os radiologistas serem capacitados para identificar fraturas de acordo com protocolos padronizados¹².

Mesmo assintomáticas, as fraturas vertebrais estão associadas com maior morbidade, incluindo incapacidade funcional¹³, redução da qualidade de vida¹⁴ e maior risco de novas fraturas^{15,16}, além do risco aumentado de mortalidade^{17,18}. A presença de uma fratura vertebral é suficiente para estabelecer o diagnóstico da osteoporose e implica início de tratamento específico para reduzir o risco de nova fratura, independente da densidade mineral óssea (DMO)^{19,20}.

A prevalência de fratura vertebral é conhecida em diferentes países²¹⁻²⁴. Estudos de prevalência fornecem dados importantes sobre a idade, sexo e influências geográficas na ocorrência de fraturas. No entanto existem limitações metodológicas quanto à interpretação e comparação dos resultados de estudos transversais, incluindo conclusões imprecisas sobre a causalidade e a relação temporal, uma vez que essas fraturas podem ter ocorrido vários anos antes do diagnóstico radiográfico. Portanto a avaliação da incidência de fraturas vertebrais em estudo longitudinal é extremamente relevante para conhecer as diferentes frequências de fratura vertebral por osteoporose em populações distintas.

Em contraste com a fratura de quadril, entretanto, dados longitudinais prospectivos sobre a incidência de fraturas vertebrais são escassos e provenientes de países desenvolvidos²⁵⁻²⁷. Além disso, alguns estudos descreveram apenas a incidência de fraturas vertebrais clinicamente diagnosticadas, o que subestima a verdadeira frequência da doença⁸, uma vez que as fraturas clínicas representam uma minoria dos casos confirmados radiograficamente. O subdiagnóstico dessas deformidades também subestima seu verdadeiro impacto na morbimortalidade.

Assim, o presente estudo teve como objetivo determinar a incidência de fraturas vertebrais osteoporóticas, diagnosticadas por radiografia, bem como identificar os principais fatores de risco (incluindo parâmetros clínicos, laboratoriais e DMO) para fraturas vertebrais em idosos brasileiros da comunidade em uma amostra de base populacional.

2 OBJETIVOS

a) Determinar, em um estudo de coorte prospectivo, a incidência de fraturas vertebrais por osteoporose, diagnosticadas por radiografia, em uma amostra de base populacional de idosos brasileiros da comunidade.

b) Identificar os preditores de nova fratura vertebral em idosos brasileiros da comunidade, entre os principais parâmetros relacionados ao metabolismo ósseo, a saber:

- Fatores clínicos de risco para osteoporose e para fratura por fragilidade óssea, incluindo idade, raça, tempo de menopausa, fratura prévia, história familiar de fratura em parente de primeiro grau, tabagismo atual, etilismo, índice de massa corporal, atividade física, quedas, ingestão de cálcio, diabetes mellitus.
- Densidade mineral óssea de coluna e fêmur proximal.
- Variáveis laboratoriais, incluindo níveis séricos de 25-hidroxivitamina D (25OHD), hormônio da paratireoide (PTH intacto) e marcadores da remodelação óssea - propeptídeo N-terminal do colágeno tipo I (P1NP) e telopeptídeo-C do colágeno tipo I (CTX).

3 MÉTODOS

3.1 População do Estudo *São Paulo Ageing & Health* (SPAH)

De junho de 2005 a julho de 2007, 1.025 idosos da comunidade, com 65 anos ou mais, foram recrutados para participar em um estudo de prevalência de fraturas osteoporóticas, o SPAH Study. Detalhes sobre a metodologia foram descritos previamente²⁸. Em resumo, o projeto incluiu indivíduos com 65 anos ou mais, residentes em 66 áreas do distrito do Butantã, localizado na parte ocidental da cidade de São Paulo, sudeste do Brasil, latitude 23°32'51". Durante as primeiras fases do estudo, todos os idosos residentes no Butantã foram identificados através de registros do censo. A distribuição de características demográficas, como faixa etária, sexo e classe social, foi semelhante ao restante da população idosa brasileira³. Somente idosos independentes e ativos foram incluídos no estudo. Todos os indivíduos foram avaliados por meio de questionário específico (hábitos de vida, comorbidades), administrado por um entrevistador, testes laboratoriais, DMO por densitometria óssea e radiografias de coluna torácica e lombar realizados no mesmo dia.

Entre 2010 e 2012, todos os sujeitos do estudo foram convidados a participar de uma segunda avaliação (fase prospectiva ou análise de incidência de fratura). Os indivíduos foram recrutados por ligação telefônica e visitas domiciliares. Eles foram levados ao centro de pesquisa (Laboratório de Metabolismo Ósseo da Faculdade de Medicina da Universidade de São Paulo) por um serviço de transporte urbano contratado especificamente para o projeto. Daqueles que não retornaram para repetir

a avaliação, 132 (12,9%) indivíduos foram a óbitos, ocorridos após o primeiro estudo (2005-2007), e 168 (16,4%) não puderam ser contatados ou recusaram a participação no estudo porque estavam vivendo fora do estado de São Paulo (perda de seguimento). Os dados de mortalidade foram confirmados por certificados de óbito obtidos junto ao Programa de Aprimoramento das Informações de Mortalidade (PRO-AIM), órgão responsável pelas estatísticas vitais em São Paulo.

Dos 1.025 participantes da primeira fase (2005-2007), 725 sujeitos concordaram em participar da segunda avaliação longitudinal (2010-2012) (taxa de resposta em indivíduos vivos, 81,2%). Dezoito (1,8%) indivíduos foram excluídos por ausência de dados (não realizaram a segunda radiografia) ou diagnóstico recente de câncer, condição conhecidamente associada a fraturas patológicas. Dessa forma, 707 indivíduos (69,0% da coorte original) foram incluídos nessa fase prospectiva do estudo (Figura 1).

O estudo foi aprovado pelo Comitê de Ética da Faculdade de Medicina da Universidade de São Paulo, e todos os participantes assinaram termo de consentimento informado (Anexo A).

Figura 1 - População do estudo SPAH

3.2 Definição de Fratura Incidente

As fraturas vertebrais foram avaliadas por meio de radiografia da coluna torácica e lombar em perfil. Os exames da avaliação inicial e do seguimento foram realizados de acordo com protocolos padronizados (distância tubo-filme de 40 polegadas, feixe de raios X centrados em T7 e L2). Para a identificação da fratura vertebral, todas as imagens foram analisadas concomitantemente por dois reumatologistas com experiência na avaliação de fratura. Os examinadores avaliaram cada imagem das vértebras T4-L4 para decidir se havia fratura utilizando o método semiquantitativo (SQ)²⁹. Apenas vértebras visualizadas adequadamente foram incluídas na análise. A reprodutibilidade do método entre os observadores foi

analisada em uma subamostra aleatória de 60 radiografias, avaliadas de forma independente pelos dois examinadores. A concordância entre eles foi de 96% (*kappa* interobservador: 0,83).

Na segunda radiografia, cada vértebra com fratura foi classificada de acordo com a gravidade segundo a escala SQ, em que uma fratura leve (grau 1) significa redução de 20-25% da altura anterior, média e/ou posterior em relação ao corpo vertebral adjacente; fratura moderada (grau 2), significa redução de 26-40% em qualquer altura; e fratura grave (grau 3), redução de mais de 40% em qualquer altura vertebral²⁹. Na presença de fratura, a radiografia basal também foi avaliada e, caso a fratura já estivesse presente, era considerada fratura prevalente. Dessa forma, definia-se uma fratura nova ou incidente se a vértebra fosse normal na primeira radiografia e qualquer uma das três alturas vertebrais (anterior, central ou posterior) mostrasse diminuição de pelo menos 20% da altura absoluta em relação ao primeiro exame. Além disso, também se definiu fratura incidente quando, na comparação entre as radiografias, houvesse alteração na morfologia do corpo vertebral resultando em maior grau de fratura (graus 2-3) na segunda radiografia, caso a vértebra já apresentasse fratura no exame inicial.

3.3 Fatores de Risco para Fratura Incidente

Os preditores de nova fratura vertebral foram investigados entre as variáveis da avaliação basal (2005-2007) – parâmetros clínicos, laboratoriais e DMO.

3.1.1 Variáveis clínicas

No estudo de prevalência, dados clínicos relacionados ao estilo de vida dos participantes foram obtidos através de questionário específico, incluindo informações como: tabagismo, consumo de álcool, história pessoal de fratura por fragilidade após 50 anos, história familiar de fratura de quadril em parentes de primeiro grau, quedas recorrentes no último ano, escore de atividade física, ingestão de cálcio, idade da menopausa, comorbidades e medicações (incluindo suplementos de cálcio e vitamina D, estrogênio e bisfosfonatos). Detalhes da metodologia de coleta dessas informações foram descritos previamente²⁸.

Altura, peso e índice de massa corporal (IMC) de cada um dos participantes foram obtidos utilizando protocolos padronizados²⁸.

3.1.2 Variáveis laboratoriais

As amostras de sangue foram coletadas em jejum (de oito a 10 horas) e centrifugadas, aliquotadas e armazenadas a -70°C até a análise. Níveis séricos de creatinina foram determinados utilizando métodos laboratoriais automatizados. A taxa de filtração glomerular (TFG) foi estimada pela equação de Cockcroft-Gault³⁰. A concentração sérica de 25OHD foi medida utilizando a técnica de radioimunoensaio (DiaSorin, Stillwater, MN, EUA), com limite inferior de detecção de 5 ng/mL. Os coeficientes de variação intra e interensaio em nosso laboratório foram 10,5% e 17,8%, respectivamente. As concentrações plasmáticas do PTH intacto foram determinadas por ensaio imunorradiométrico (ELSA - PTH, CIS bio international, França), com valores de referência de 11-65 pg/mL.

Marcadores de remodelação óssea no soro – P1NP e CTX – foram analisados por eletroquimioluminescência (E411, Roche Diagnostics[®], Mannheim, Alemanha). Os coeficientes de variação para P1NP e CTX foram 2,2% e 2,5%, respectivamente.

3.1.3 Densidade mineral óssea

A medida da DMO através de absorciometria por dupla emissão de raios X (*Dual X-ray Absorptiometry - DXA*) foi realizada em coluna lombar, colo do fêmur e quadril total, utilizando o equipamento DXA Hologic QDR 4500A (Hologic Inc. Bedford, MA, EUA, modelo Discovery), como descrito anteriormente²⁸. As mínimas variações significativas (MVS) foram 0,033 g/cm² na coluna lombar, 0,047 g/cm² no colo do fêmur e 0,039 g/cm² no quadril total.

3.4 Análise Estatística

Incidência: cada sujeito teve uma data de entrada na coorte, correspondendo à data do exame basal (2005-2007), e uma data de saída, que foi aquela da segunda visita/radiografia (2010-2012). Na análise de incidência para cada indivíduo, o período de exposição (risco) foi calculado como o intervalo de tempo em meses entre essas duas datas. A incidência foi expressa como o número de indivíduos com pelo menos uma fratura incidente por 1000 pessoas/ano em risco, estratificados por sexo e categorias de faixa etária de 10 anos. Intervalos de confiança de 95% (IC 95%) foram calculados utilizando a fórmula exata de Poisson. Os resultados foram apresentados como taxas de incidência brutas e também padronizados para a distribuição etária da população idosa brasileira no ano de 2010⁶ para cada sexo. Riscos relativos (RRs) e IC 95% foram utilizados para comparar as taxas de fraturas entre os sexos.

Fatores de risco: a prevalência de qualquer preditor (variáveis da avaliação basal - 2005-2007) foi reportada de acordo com análise descritiva para os indivíduos com e sem fratura vertebral incidente, separadamente para cada sexo. Os seguintes parâmetros foram analisados: idade (variável contínua e categórica), raça (categórica), altura (contínua), peso (contínua), IMC (contínua), tempo desde a menopausa (contínua), tabagismo (categórica), ingestão alcoólica (dicotômica), quedas recorrentes (dicotômica), escore de atividade física (categórica), história familiar de fratura (dicotômica), ingestão de cálcio na dieta (dicotômica), diabetes mellitus (dicotômica), outras causas da osteoporose secundária (dicotômica), fratura por fragilidade prévia (dicotômica), uso de medicamentos antifratura (dicotômica), TFG (contínua), PTH (contínua), 25OHD (contínua e categórica), CTX (contínua e quartis), PINP sérico (contínuo e quartis), diagnóstico de osteoporose (categórica) e DMO da coluna lombar e fêmur proximal (contínua e categórica). Para avaliar as diferenças potencialmente significativas nas características basais entre indivíduos com e sem fratura, foram utilizados, separadamente para cada sexo, os seguintes testes: do quiquadrado, de Fisher, da razão de verossimilhanças, teste t de Student e de Mann-Whitney. Considerando-se uma possível menor magnitude de associação de alguns fatores de risco potenciais (que não atingem significância estatística com um valor de $p < 0,05$ por causa da baixa frequência na população do estudo), a significância na análise univariada foi considerada quando $p < 0,10$ (bicaudal). Todas as associações de fatores de risco e fratura incidente estatisticamente significativas na análise univariada foram selecionadas para a regressão multivariada. Modelos de regressão de Poisson foram construídos para testar a independência entre os fatores de risco e derivar funções de risco contínuas, separadamente para homens e

mulheres. Dada a colinearidade entre os sítios de DMO, estes foram adicionados em diferentes modelos de regressão de Poisson, sendo selecionado o melhor deles. Os resultados foram apresentados como risco estimado de nova fratura vertebral e expressos como RRs com os respectivos IC 95%.

Análise de não participação: dos 1.025 participantes na coorte original (2005-2007), 707 foram incluídos na fase prospectiva (2010-2012). Para avaliar o potencial impacto da não participação na taxa de incidência, foram avaliadas as diferenças nas variáveis clínicas, laboratoriais e DMO da avaliação inicial entre os participantes (N = 707) e não participantes (N = 318), pressupondo que a relação entre fatores de risco e fratura subsequente foi similar em ambos os grupos²⁶. Para descartar a possível influência da maior mortalidade sobre as diferenças entre os dois grupos, ou seja, aqueles com maior risco podem ter morrido, foi realizada também a análise excluindo os 132 óbitos durante o período do estudo.

STATA, versão 11.0 (Stata Corp, College Station, Tex), foi utilizado para calcular as taxas de incidência. Fatores de risco e IC 95% foram gerados pelo SPSS, versão 20.0 para Windows.

4 RESULTADOS

4.1 Características da População

Um total de 707 indivíduos (449 mulheres e 258 homens), com 65 anos ou mais, foi incluído na análise. A renda familiar média mensal foi de R\$ 1.098,48 $\pm$ 850,96, sendo que 261 (36,9%) tinham uma renda familiar mensal equivalente a um salário mínimo (R\$724,00). O tempo médio de escolaridade foi 2,9 anos, com 206 (29,2%) sujeitos com até três anos de tempo de escolaridade e 218 (30,8%) analfabetos. Por causa da variabilidade nas datas da visita inicial (2005-2007) e da segunda avaliação (2010-2012), o tempo de seguimento foi variável entre os participantes (2,2 - 6,5 anos, média de 4,3 $\pm$ 0,8 anos).

4.2 Taxas de Incidência

De 9.191 corpos vertebrais (T4-L4) potencialmente legíveis, 79 (0,9%) vértebras não foram adequadamente visíveis nas radiografias do estudo basal e 53 (0,6%) vértebras não estavam visíveis na segunda radiografia. Das 79 vértebras ilegíveis nas primeiras radiografias, 66 (83,5%) estavam localizadas no segmento T4-T6 e 5 (6,3%) no segmento L3-L4. Na segunda avaliação radiográfica, a frequência de corpos vertebrais não visíveis também foi maior nos segmentos T4-T6 (42/53, 79,2%) e L3-L4 (7/53, 13,2%).

Setenta e sete (17,1%) mulheres e 34 (13,2%) homens apresentaram ao menos uma nova fratura vertebral durante o seguimento. No total, 63 (11,2%) indivíduos

apresentaram uma única fratura incidente durante o período do estudo, 32 tinham duas fraturas, 10 tinham três, três tinham quatro e um sujeito apresentou cinco, seis ou sete fraturas cada um. As taxas de fratura vertebral por sexo e idade são apresentadas na Tabela 1 e Gráfico 1. As incidências brutas de fratura vertebral foram 40,3/1000 pessoas/ano em mulheres e 30,6/1000 pessoas/ano em homens. As taxas de incidência padronizadas para a população brasileira com 65 anos ou mais foram 44,0/1000 pessoas/ano em mulheres e 32,6/1000 pessoas/ano em homens.

Em ambos os sexos, a incidência aumentou significativamente no grupo com idade mais avançada (≥ 80 anos). A incidência foi maior em mulheres do que em homens nos grupos entre 70-79 anos (33,1/1000 pessoas/ano e 22,4/1000 pessoas/ano, respectivamente) e 80 anos ou mais (97,5/1000 pessoas/ano e 57,9/1000 pessoas/ano), mas discretamente menor naqueles com 65-69 anos (35,3/1000 pessoas/ano em mulheres e 36,5/1000 pessoas/ano em homens) (Tabela 1 e Gráfico 1). A razão de risco entre os sexos (mulher: homem) foi 1,21, mas tal proporção aumentou com a idade, embora sem significância estatística. Excluindo fraturas leves (grau 1), 34 (7,6%) mulheres e 14 (5,4%) homens apresentaram nova fratura vertebral moderada (grau 2) ou grave (grau 3). A incidência de fratura moderada/grave foi 17,8/1000 pessoas/ano em mulheres e 12,6/1000 pessoas/ano em homens. As taxas de incidência de fratura moderada/grave, padronizadas para a população brasileira com 65 anos ou mais, foram 18,6/1000 pessoas/ano em mulheres e 14,9/1000 pessoas/ano em homens.

Tabela 1 - Incidência de fratura vertebral radiográfica por sexo e idade

Idade (anos)	Mulheres				Homens				Risco relativo mulher: homem [IC 95%]
	Sujeitos (n)	Pessoas-ano sob risco	Sujeitos com fratura (n)	Incidência (/1000) [IC 95%]	Sujeitos (n)	Pessoas-ano sob risco	Sujeitos com fratura (n)	Incidência (/1000) [IC 95%]	
65-69	130	538	19	35,3 [22,4-55,4]	90	384	14	36,5 [21,6-61,6]	1,08 [0,54-2,15]
70-79	275	1178	39	33,1 [24,2-45,3]	143	625	14	22,4 [13,3-37,8]	1,38 [0,75-2,55]
≥ 80	44	195	19	97,5 [62,2-152,8]	25	104	6	57,9 [26,0-128,8]	0,97 [0,37-2,53]
Todos	449	1910	77	40,3 [32,2-50,4]	258	1113	34	30,6 [21,8-42,8]	1,21 [0,80-1,81]

Gráfico 1 - Incidência de fratura vertebral radiográfica por sexo e idade

4.3 Preditores de Nova Fratura Vertebral

As variáveis da avaliação inicial (2005-2007) estratificadas por sexo e fratura incidente são apresentadas nas Tabelas 2 e 3. A análise univariada demonstrou que mulheres com nova fratura vertebral, quando comparadas àquelas sem fratura incidente, eram mais velhas, frequentemente da raça branca, tinham menor altura, peso e IMC e maior tempo de menopausa. Além disso, apresentavam maior prevalência de fratura prévia, menor TGF, maiores valores de CTX (na análise categórica por quartis) e menor DMO em coluna lombar, colo do fêmur e quadril total. Homens com nova fratura vertebral no seguimento apresentavam maior ingestão de álcool, maior frequência de fratura prévia por osteoporose e maiores valores de CTX (na análise por quartis).

Tabela 2 - Características clínicas da avaliação inicial (2005-2007) de indivíduos com e sem nova fratura vertebral

Características básicas	Mulheres		Homens		P ^a
	Com nova fratura (n=77)	Sem nova fratura (n=372)	Com nova fratura (n=34)	Sem nova fratura (n=224)	
Idade (anos)	75,4 (6,3)	72,4 (4,2)	73,3 (5,9)	72,2 (4,4)	0,293
Raça - n (%)					0,666
Branca	56 (19,8)	227 (80,2)	23 (13,9)	143 (86,1)	
Não branca	21 (12,7)	145 (87,3)	11 (12,0)	81 (88,0)	
Altura (cm)	149,1 (6,5)	150,5 (5,9)	163,2 (9,3)	162,5 (7,2)	0,696
Peso (kg)	60,8 (12,7)	66,8 (13,3)	69,9 (11,2)	70,6 (12,4)	0,741
IMC(kg/m ²)	27,3 (5,2)	29,4 (5,3)	26,2 (3,4)	26,7 (4,2)	0,508
Tempo desde menopausa (anos)	27,3 (6,9)	23,6 (6,8)	NA	NA	
Uso atual de estrogênio - n (%)	6 (18,2)	27 (81,8)	NA	NA	
Tabagismo - n (%)					0,589
Atual	9 (18,8)	39 (81,2)	3 (9,4)	29 (90,6)	
Passado	18 (16,4)	92 (83,6)	20 (15,2)	112 (84,8)	
Nunca	50 (17,2)	241 (82,8)	11 (11,7)	83 (88,3)	
Etilismo (≥3 unidades/dia) - n (%)	0	2 (100,0)	4 (28,6)	10 (71,4)	0,096
Quedas recorrentes (≥ 2 quedas no último ano) - n (%)	17 (23,3)	56 (76,7)	2 (11,1)	16 (88,9)	> 0,999
Escore de atividade física - n (%)					0,389
Baixo	6 (28,6)	15 (71,4)	3 (12,5)	21 (87,5)	
Moderado	55 (18,3)	246 (81,7)	20 (11,4)	155 (88,6)	
Alto	16 (12,6)	111 (87,4)	11 (18,6)	48 (81,4)	

Continua

Conclusão

Características básicas	Mulheres		Homens		P ^a
	Com nova fratura (n=77)	Sem nova fratura (n=372)	Com nova fratura (n=34)	Sem nova fratura (n=224)	
História familiar de fratura - n (%)	6 (12,8)	41 (87,2)	2 (13,3)	13 (86,7)	0,942
Ingestão diária de lacteos (mg/dia)	414,6 (281,0)	470,6 (308,6)	343,9 (225,7)	403,0 (319,5)	0,300
Diabetes mellitus - n (%)	13 (14,4)	77 (85,6)	3 (7,7)	36 (92,3)	0,272
Outras comorbidades ^b - n (%)	4 (15,4)	22 (84,6)	1 (11,1)	8 (88,9)	> 0,999
Qualquer fratura prévia ^c - n (%)	23 (23,5)	75 (76,5)	10 (22,7)	34 (77,3)	0,040
Fratura vertebral prévia (moderada/grave) - n (%)	15 (23,1)	50 (76,9)	6 (19,4)	25 (80,6)	0,266
Fratura não vertebral prévia - n (%)	11 (25,6)	32 (74,4)	5 (31,2)	11 (68,8)	0,044
Uso atual de suplementos de cálcio - n (%)	10 (25,0)	30 (75,0)	0	1 (100,0)	> 0,999
Uso atual de suplementos de vitamina D - n (%)	6 (28,6)	15 (71,4)	0	2 (10,0)	> 0,999
Uso atual de bisfosfonato - n (%)	7 (25,9)	20 (74,1)	0	1 (100,0)	> 0,999

Variáveis categóricas foram expressas como n (%) e variáveis contínuas como média (IDP).

^a Valores de P: comparação de médias (teste t Student ou teste de Mann-Whitney) ou proporções (teste de qui-quadrado, teste de Fisher ou teste da razão de verossimilhanças).^b Hipertireoidismo, hipoparatiroidismo primário, asma/doença pulmonar obstrutiva crônica, doença hepática crônica, hipertensão, doença cerebrovascular e infarto do miocárdio^c Incluindo fraturas não vertebrais e vertebrais moderadas/graves

IMC = Índice de Massa Corporal; NA = não aplicável

Tabela 3 - Variáveis laboratoriais e DMO da avaliação inicial (2005-2007) de indivíduos com e sem nova fratura vertebral

Características basais	Mulheres		<i>P</i> ^a	Homens		<i>P</i> ^a
	Com nova fratura (n=77)	Sem nova fratura (n=372)		Com nova fratura (n=34)	Sem nova fratura (n=224)	
TFG (mL/min/1,73 m ²)	50,7 (16,8)	61,3 (18,9)	<0,001	57,0 (17,2)	60,5 (17,0)	0,300
PTH (pg/mL)	43,2 (20,1)	40,0 (16,6)	0,144	39,0 (20,0)	36,2 (16,3)	0,400
25OHD (categorias), n (%)			0,569			0,729
< 20 ng/mL	42 (15,8) ^b	224 (84,2) ^c		17 (13,9) ^d	105 (86,1) ^e	
21 - 29 ng/mL	27 (19,9) ^b	109 (80,1) ^c		2 (13,5) ^d	77 (86,5) ^e	
> 30 ng/mL	7 (15,6) ^b	38 (84,4) ^c		4 (9,3) ^d	39 (90,7) ^e	
25OHD (ng/mL)	19,4 (9,4)	18,8 (9,0)	0,578	20,5 (9,6)	22,4 (9,2)	0,300
CTX (quartis) - n (%)			0,093			0,047
Q1-Q3	52 (15,6)	282 (84,4) ^f		21 (11,1) ^g	169 (88,9) ^h	
Q4 ^k	25 (22,5)	86 (77,5) ^f		13 (21,0) ^g	49 (79,0) ^h	
CTX (ng/mL)	0,447 (0,241)	0,408 (0,238)	0,184	0,389 (0,180)	0,335 (0,203)	0,149
P1NP (quartis) - n (%)			0,157			0,267
Q1-Q3	53 (15,8)	283 (84,2) ⁱ		23 (12,0)	169 (88,0) ^j	
Q4 ^l	24 (21,6)	87 (78,4) ⁱ		11 (17,5)	52 (82,5) ^j	
P1NP (ng/mL)	46,55 (26,04)	44,19 (29,59)	0,516	44,82 (24,32)	39,25 (21,55)	0,169

Continua

Características basais	Mulheres		Homens		P ^a	Conclusão
	Com nova fratura (n=77)	Sem nova fratura (n=372)	Com nova fratura (n=34)	Sem nova fratura (n=224)		
DMO (classificação) - n (%)					0,099	0,351
Normal	6 (14,3)	36 (85,7)	5 (11,4)	39 (88,6)		
Osteopenia	19 (12,4)	134 (87,6)	22 (15,9)	116 (84,1)		
Osteoporose	52 (20,5)	202 (79,5)	7 (9,2)	69 (90,8)		
DMO coluna lombar (g/cm ²)	0,773 (0,158)	0,834 (0,172)	0,993 (0,187)	1,009 (0,188)	0,004	0,654
DMO colo do fêmur (g/cm ²)	0,607 (0,114)	0,666 (0,123)	0,731 (0,093)	0,751 (0,136)	< 0,001	0,280
DMO quadril total (g/cm ²)	0,722 (0,120)	0,804 (0,131)	0,912 (0,117)	0,938 (0,140)	< 0,001	0,309

Variáveis categóricas foram expressas como n (%) e variáveis contínuas como média (IDP).

^a Valores de P: comparação de médias (teste t student ou teste de Mann-Whitney) ou proporções (teste de qui-quadrado, teste de Fisher ou teste da razão de verossimilhanças).

^b n=76; ^c n=371; ^d n=33; ^e n=221; ^f n=368; ^g n=34; ^h n=218; ⁱ n=370; ^j n=221

^k >0,529 ng/mL em mulheres e >0,440 ng/mL em homens; ^l >55,49ng/mL em mulheres e >47,09 ng/mL em homens.

TFG = Taxa de Filtração Glomerular, PTH: paratormônio, 25OHD = 25 hidroxivitamina D, CTX = telopeptídeo C- terminal do colágeno tipo I, PINP = propeptídeo N-terminal do colágeno tipo I, Q = quartil, DMO = Densidade Mineral Óssea.

Após ajuste para as demais variáveis significantes na análise univariada, a regressão multivariada de Poisson nas mulheres resultou em três possíveis modelos finais de preditores independentes de fratura vertebral: a) idade (RR 2,46, IC 95% 1,66-3,65, $p < 0,001$, para cada aumento de 10 anos), fratura prévia por osteoporose (RR 1,65, IC 95% 1,00-2,71, $p=0,049$) e DMO da coluna lombar (RR 1,21, IC 95% 1,03-1,41, $p = 0,017$, para cada redução de 1 DP); b) idade (RR 2,25, IC 95% 1,52-3,34, $p < 0,001$) e DMO do colo do fêmur (RR 1,42, IC 95% 1,11-1,81, $p = 0,006$); e c) idade (RR 2,11, IC 95% 1,41-3,15, $p < 0,001$) e DMO do quadril total (RR 1,56, IC 95% 1,21-2,01, $p = 0,001$) (Gráfico 2).

Embora os RRs tenham atingido significância limítrofe, o maior quartil de CTX ($> 0,440$ ng/mL) (RR 1,96, IC 95% 0,98-3,91, $p = 0,057$) e a presença de fratura prévia (RR 2,10, IC 95% 1,00-4,39, $p = 0,050$) foram fatores de risco para nova fratura vertebral em homens após ajustes para idade, IMC, TGF, DMO e variáveis significantes na análise univariada (Gráfico 2).

Gráfico 2 - Preditores independentes de nova fratura vertebral radiográfica em mulheres e homens do estudo SPAH

4.4 Análise de Não Participação

Em comparação com os participantes da segunda avaliação (2010-2012), as mulheres que não participaram do estudo eram mais velhas ($74,9 \pm 6,6$ *versus* $72,9 \pm 4,8$ anos, $p < 0,001$), tinham menor IMC ($28,1 \pm 5,4$ *versus* $29,1 \pm 5,3$ kg/m², $p = 0,035$), menor escore de atividade física ($22,2\%$ *versus* $4,7\%$, $p < 0,001$), maior prevalência de diabetes mellitus ($29,0\%$ *versus* $20,0\%$, $p = 0,02$), menor frequência de uso de medicamentos antifratura ($0,6\%$ *versus* $6,9\%$, $p = 0,001$), menor TFG ($54,7 \pm 19,0$ *versus* $59,5 \pm 19,0$ mL/min/1,73 m², $p = 0,007$), maior PTH ($48,3 \pm 34,8$ *versus* $40,6 \pm 17,3$ pg/mL, $p = 0,041$) e menores níveis de 25OHD ($16,9 \pm 8,5$ *versus* $18,9 \pm 9,1$ ng/mL, $p = 0,011$). Para homens, a comparação revelou que os não participantes eram mais velhos ($73,6 \pm 5,6$ *versus* $72,3 \pm 4,7$ anos, $p = 0,023$), geralmente de raça branca ($76,1\%$ *versus* $64,3\%$, $p = 0,020$), tinham maior frequência de quedas recorrentes ($15,5\%$ *versus* $7,0\%$, $p = 0,007$), menor escore de atividade física ($19,7\%$ *versus* $9,3\%$, $p = 0,011$), menores níveis de 25OHD ($19,8 \pm 10,1$ *versus* $22,2 \pm 9,3$ ng/mL, $p = 0,018$), maiores valores de CTX ($0,425 \pm 0,261$ *versus* $0,342 \pm 0,201$ ng/mL, $p = 0,010$) e menor DMO no quadril total ($0,903 \pm 0,166$ *versus* $0,935 \pm 0,137$ g/cm², $p = 0,043$). No entanto, quando os óbitos foram excluídos, a maioria dessas diferenças tornou-se não significante (Tabela 4).

Tabela 4 - Características de participantes e não participantes (excluindo óbitos) da fase longitudinal (2010-2012) do estudo SPAH

Características basais	Participação			
	Mulheres		Homens	
	Sim (n=449)	Não (n=109)	Sim (n=258)	Não (n=77)
			<i>P^a</i>	<i>P^a</i>
Idade (anos)	72,9 (4,8)	73,7 (5,9)	0,156	72,3 (4,7)
Raça branca - n (%)	283 (63,0)	73 (67,0)	0,053	166 (64,3)
IMC - kg/m ²	29,1 (5,3)	29,1 (5,1)	0,980	26,6 (4,1)
Tabagismo - n (%)			0,580	
Atual	48 (10,7)	11 (10,0)		32 (12,4)
Passado	110 (24,5)	32 (29,4)		132 (51,2)
Nunca	291 (64,8)	66 (60,6)		94 (36,4)
Etilismo (≥ 3 unidades/dia) - n (%)	2 (0,5)	0	> 0,999	14 (5,4)
Quedas recorrentes (≥ 2 quedas no último ano) - n (%)	73 (16,3)	17 (15,6)	0,866	18 (7,0)
Escore de atividade física- n (%)			< 0,001	
Baixo	21 (4,7)	18 (16,5)		24 (9,3)
Moderado	301 (67,0)	73 (67,0)		175 (67,8)
Alto	127 (28,3)	18 (16,5)		59 (22,9)
História familiar de fratura - n (%)	47 (10,5)	9 (8,3)	0,337	15 (5,8)
Ingestão diária de lácteos (mg/dia)	460,9 (304,5)	414,3 (274,5)	0,144	395,2 (309,1)
Diabetes mellitus - n (%)	90 (20,0)	26 (23,9)	0,385	39 (15,1)
Fratura não vertebral prévia - n (%)	43 (9,6)	11 (10,1)	0,870	16 (6,2)

Continua

Características basais	Participação				Conclusão	
	Mulheres		Homens			
	Sim (n=449)	Não (n=109)	Sim (n=258)	Não (n=77)		
			<i>P^a</i>		<i>P^a</i>	
Fratura vertebral prévia (moderada/grave) - n (%)	119 (26,5)	24 (22,0)	0,336	74 (28,7)	23 (29,9)	0,840
Uso atual de medicação antifratura - (%) ^b	31 (6,9)	0	0,005	1 (0,4)	0	> 0,999
TFG (mL/min/1,73 m ²)	59,5 (19,0)	56,7 (17,4)	0,288	60,0 (17,0)	59,6 (15,7)	0,759
PTH (pg/mL)	40,6 (17,3)	44,1 (33,2)	0,864	36,6 (16,8)	40,1 (24,1)	0,471
25OHD (ng/mL)	18,9 (9,1) ^c	17,0 (7,4)	0,024	22,2 (9,3) ^d	20,2 (9,7)	0,110
DMO (classificação) - n (%)			0,457			0,350
Normal	42 (9,4)	14 (12,8)		44 (17,1)	18 (23,4)	
Osteopenia	153 (34,1)	56 (51,4)		138 (53,5)	24 (31,2)	
Osteoporose	254 (56,6)	39 (35,8)		76 (29,5)	35 (45,5)	
DMO coluna lombar (g/cm ²)	0,824 (0,171)	0,867 (0,198)	0,023	1,006 (0,188)	1,012 (0,213)	0,830
DMO colo do fêmur (g/cm ²)	0,656 (0,123)	0,671 (0,125)	0,266	0,749 (0,131)	0,762 (0,168)	0,528
DMO quadril total (g/cm ²)	0,790 (0,133)	0,796 (0,138)	0,676	0,935 (0,137)	0,934 (0,162)	0,987

Variáveis categóricas foram expressas como n (%) e variáveis contínuas como média (IDP).

^a Valores de P: comparação de médias (teste t Student ou teste de Mann-Whitney) ou proporções (teste de qui-quadrado, teste de Fisher ou teste da razão de verossimilhanças).

^b Incluindo suplementos de cálcio e/ou vitamina D, bisfosfonatos ou estrogênio.

^c_n = 447; ^d_n = 240.

IMC = Índice de Massa Corporal; TFG = Taxa de Filtração Glomerular; PTH = paratormônio; 25OHD = 25 hidroxivitamina D.

5 DISCUSSÃO

Este é o primeiro estudo de base populacional que determinou a incidência de fratura vertebral em coorte latino-americana. Entre os idosos brasileiros da comunidade, seguidos por 4,3 anos, 21% das mulheres e 16% dos homens apresentaram nova fratura vertebral radiográfica.

SPAH é um estudo coorte de base populacional que se diferencia pela avaliação de uma população homogênea e bem caracterizada de idosos residentes na comunidade, com características (idade, sexo, distribuição de classe social) semelhantes às da população brasileira com mais de 65 anos de idade definidas pelo censo do Instituto Brasileiro de Geografia e Estatística (IBGE)³. Na fase longitudinal, a taxa de adesão ao estudo entre os indivíduos vivos foi elevada (81,2%). O diagnóstico da fratura foi realizado através de radiografia de coluna, independente de sintomas: já que apenas aproximadamente 30% das fraturas vertebrais são sintomáticas⁸, somente a identificação radiográfica permite o reconhecimento da verdadeira frequência da doença. Diferente de estudos epidemiológicos baseados em banco de dados ou informações de prontuários médicos^{8,31}, este estudo empregou protocolos rigorosamente consistentes para definir fratura incidente com base na comparação entre a primeira e a segunda radiografias, reduzindo a possibilidade de falso-positivos. Além disso, em comparação com dados epidemiológicos prévios³²⁻³⁴, neste estudo foi investigado um conjunto mais amplo de potenciais fatores de risco para fraturas vertebrais, abrangendo concomitantemente variáveis clínicas, laboratoriais e DMO.

De acordo com a idade, a taxa de incidência de fraturas vertebrais em idosos brasileiros foi 1,5-6 vezes maior do que a observada em países europeus, incluindo a Escandinávia, onde a incidência parece ser maior do que no resto da Europa²⁶. A comparação entre os diferentes estudos, no entanto, é dificultada pela ausência de consenso acerca do melhor critério radiográfico para o diagnóstico de fratura. Diferentes metodologias utilizam distintos pontos de corte para definir fratura incidente, o que afeta a sensibilidade e a especificidade dos critérios e cria considerável discordância entre os dados de incidência^{35,36}.

Porém as taxas de incidência anuais reportadas aqui foram muito semelhantes às encontradas na população asiática³⁷⁻³⁹, em especial no Japão. A incidência anual em mulheres japonesas entre 70-79 anos foi 40/1000 pessoas/ano e 84/1000 pessoas/ano em mulheres com mais de 80 anos. É importante ressaltar que o estudo japonês utilizou o mesmo critério radiológico de fratura (SQ) aplicado no estudo SPAH e ambos tiveram tempos de seguimento similares²⁷.

Conforme previamente demonstrado, o método SQ teve uma excelente concordância interobservador para o diagnóstico de deformidade vertebral na população brasileira³⁹. De fato, esta abordagem tem sido utilizada em vários estudos recentes⁴⁰⁻⁴² e recomendada para o diagnóstico de fratura vertebral pela Sociedade Internacional de Densitometria Clínica⁴³. Diferente do critério morfométrico, que está sujeito a maiores variações intra e interobservador pela subjetividade inerente ao método (colocação dos pontos de reparo nas bordas do corpo vertebral), a abordagem SQ tem a vantagem de permitir a distinção entre fraturas e deformidades vertebrais devido a outras causas, como osteoartrite e doença de Scheuermann⁴⁴. A metodologia SQ apresenta maior sensibilidade para o diagnóstico da fratura, o que pode ser

explicado, em grande parte, pela presença de deformidades vertebrais menores que não preenchem o critério morfométrico de definição de fratura, mas são classificadas como fraturas leves pela metodologia SQ⁴⁵. Reiterando a importância clínica da utilização de um método com boa sensibilidade para a adequada identificação de fraturas, uma recente meta-análise (que incluiu os grupos placebo de quatro ensaios clínicos em osteoporose) mostrou que fraturas vertebrais leves estão associadas com o aumento do risco de novas fraturas vertebrais⁴⁶.

É possível que existam genuínas diferenças populacionais que contribuam para as discrepâncias nas taxas de incidência de fratura vertebral entre a população do estudo SPAH e outros grupos. Uma variabilidade significativa da incidência de fraturas de quadril tem sido descrita mesmo em diferentes áreas geográficas dentro do território brasileiro, com taxas superiores no sul em relação ao norte do país⁴⁷⁻⁴⁹. Essa diferença pode ser explicada pelo tamanho do território, a substancial miscigenação étnica e hábitos de vida distintos do povo brasileiro de acordo com a região do país. Apesar disso, a população da cidade de São Paulo (onde foi realizado o estudo SPAH) é caracterizada por uma mistura de europeus (brancos portugueses e italianos), brasileiros nativos, descendentes de japoneses e grande número de emigrantes de outras áreas do país. São Paulo seria a cidade brasileira com uma população que parece ser mais representativa da miscigenação étnica, que define o povo brasileiro, do que outras localidades do país.

Em concordância com estudos prévios^{27,31}, a proporção de mulheres com nova fratura no estudo SPAH aumentou na faixa etária mais avançada. Essa tendência também foi observada em homens. Além disso, a incidência absoluta de fratura vertebral foi menor nos homens do que nas mulheres, exceto na faixa etária

mais jovem (65-69 anos). No entanto a razão de risco mulher/homem não atingiu diferença estatística significativa em todas as faixas etárias. Em relação à menor diferença de incidência entre os sexos nas faixas etárias mais jovens, achados semelhantes foram observados na população do estudo Rotterdam⁵⁰.

Recentemente, foram desenvolvidos algoritmos de risco absoluto de fratura em 10 anos (FRAX[®]) com base em um perfil de fatores clínicos de risco, DMO e mortalidade específica de cada país. Os modelos mais completos disponíveis são os do Reino Unido, Suécia, Japão e EUA, desde que a epidemiologia dos principais sítios de fraturas osteoporóticas já foi bem estabelecida nesses países⁵¹. No entanto os modelos do FRAX[®] para outros países (incluindo o Brasil) são baseados apenas no risco de fratura de quadril, dada a escassez de dados epidemiológicos, e utilizam a proporção de fratura vertebral/quadril da população sueca para derivar as funções de risco para as outras fraturas osteoporóticas maiores, incluindo vertebrais⁵². Contudo a relação vertebral/quadril da Suécia foi obtida a partir de taxas de incidência de fraturas vertebrais clínicas e, portanto, FRAX[®] não leva em conta a fratura vertebral radiográfica, que é a fratura osteoporótica mais comum^{7,8}. Além disso, a razão entre fratura vertebral e quadril varia significativamente entre os países. Por exemplo, asiáticos têm uma razão entre fratura vertebral e de quadril muito mais elevada (1,7 a 6,3 de acordo com a idade) do que brancos (0,5 a 1,4)³⁷. Em idosos brasileiros, também se observa uma razão vertebral/quadril mais elevada (1,8-2,8) (dados não publicados), sugerindo que um modelo baseado na relação entre fratura vertebral e de quadril da população sueca pode subestimar o risco de fratura osteoporótica maior.

No Brasil, estudos transversais têm reportado os fatores de risco para fratura prevalente^{28,53}. SPAH é o primeiro estudo brasileiro longitudinal, com amostra de base populacional, que determinou os preditores de nova fratura vertebral radiográfica. Em mulheres, idade e DMO foram os preditores de fratura vertebral incidente. Fatores reprodutivos não foram associados ao aumento do risco de fratura vertebral. Embora o tempo de menopausa fosse associado com nova fratura na análise univariada, ele não permaneceu no modelo final de regressão após ajuste para idade. Em consonância com esse dado, o *status* menopausal também não foi associado com aumento do risco de fratura vertebral em mulheres brancas americanas com mais de 65 anos³³. Esses resultados podem ser explicados pela idade avançada da população estudada, que se sobrepõe ao tempo de menopausa e torna-se um fator de risco preponderante após os ajustes na análise multivariada. Além disso, outros fatores como a função renal (TGF) foram associados com fratura na análise univariada, mas não permaneceram significantes após ajuste para idade e DMO.

Em concordância com dados recentes^{34,41,54}, fatores de risco para fratura vertebral em homens foram menos bem caracterizados neste estudo. Tal achado pode ser explicado devido ao fato de o estudo SPAH incluir somente indivíduos idosos independentes e ativos, muitos dos quais ainda exercem atividades que requerem esforço físico. Não podemos descartar, portanto, a possibilidade de que algumas deformidades vertebrais incidentes em homens podem estar relacionadas a atividades ocupacionais envolvendo trauma, particularmente em indivíduos com idade inferior a 70 anos, faixa etária em que houve incidência absoluta de fratura semelhante em homens e mulheres. Esses achados estão de acordo com estudos anteriores^{24,28,55}. Alternativamente, o pequeno número de fraturas observado em homens reduz o

poder estatístico do estudo em demonstrar maior magnitude de associação com alguns fatores de risco na predição de fraturas. Além disso, embora o diagnóstico de fratura no estudo SPAH tenha sido baseado na rigorosa comparação de radiografias para reduzir a possibilidade de falso-positivos, algumas deformidades leves poderiam representar alterações degenerativas, muitas vezes, difíceis de serem diferenciadas de verdadeiras fraturas por fragilidade⁵⁶, mesmo na análise radiográfica comparativa. Apesar disso, nossos resultados sugerem que a frequência de fratura vertebral osteoporótica em idosos brasileiros é elevada, uma vez que a incidência de fratura moderada ou grave manteve-se alta mesmo após exclusão das deformidades grau 1.

O risco relativo de fratura vertebral para cada redução de um desvio padrão na DMO do quadril foi maior do que na DMO de coluna, um padrão observado em estudos anteriores^{23,28,32}. Essa diferença pode refletir os efeitos do envelhecimento sobre a coluna (calcificação aórtica ou osteoartrite), superestimando os valores de DMO neste sítio⁵⁷.

Independente da DMO, a remodelação óssea é apontada como preditora do risco de fratura em homens e mulheres⁵⁸⁻⁶¹, embora poucos estudos tenham sido especificamente desenhados para investigar fraturas vertebrais⁵⁷⁻⁵⁹ e existam poucos estudos em homens⁶¹. Nesta pesquisa, homens com maiores valores do marcador de reabsorção óssea (CTX) tiveram risco aumentado de fratura vertebral independente da idade, DMO, peso e escore de atividade física.

O estudo SPAH apresenta algumas limitações, incluindo o pequeno número de fraturas incidentes, particularmente em homens, o que pode ter subestimado o poder estatístico do estudo, como já mencionado. Um possível viés de seleção também pode ter resultado da falta de alguns dados laboratoriais para alguns

indivíduos. Além disso, durante o período do estudo, alguns indivíduos ($< 10\%$) estavam em uso de alguma medicação antifratura (incluindo compostos de vitamina D e bisfosfonatos) prescrita após a avaliação inicial (2005-2007), o que poderia influenciar no resultado da incidência de fratura. Entretanto isso parece pouco provável, pois a maioria dos indivíduos teve baixa adesão ao tratamento ($< 75\%$) e as frequências de utilização de medicação foram semelhantes nos grupos com e sem fratura incidente (dados não mostrados).

Uma das principais preocupações neste estudo foi a possibilidade de viés de não participação que poderia alterar as estimativas de incidência. Os indivíduos que não participaram na fase prospectiva (2010-2012) poderiam ter diferença no risco de fratura em relação aos participantes do estudo, o que tem o potencial de superestimar ou subestimar a verdadeira incidência da doença. A não participação foi relacionada basicamente a óbitos após o estudo de prevalência (2005-2007) e mudanças de endereço (fora do estado de SP). Entretanto essas diferenças não foram significantes quando os óbitos foram excluídos da comparação. Tais resultados indicam que as diferenças nos potenciais fatores de risco podem ser atribuídas a indivíduos que morreram no seguimento. Assim, o maior impacto da não participação na incidência seria provavelmente relacionado à mortalidade, ou seja, aqueles sob maior risco de fratura teriam morrido e, portanto, não eram elegíveis para participar do estudo longitudinal. De fato, idade e DMO do quadril foram os principais fatores na análise multivariada que explicaram o aumento do risco de fratura vertebral na população em estudo, e tais variáveis não foram significativamente diferentes entre participantes e não participantes vivos. Considerando que há uma relação semelhante entre fatores de risco (variáveis da avaliação inicial) e fratura subsequente entre

participantes e não participantes, esses resultados suportam a ideia de que, apesar das diferenças nos parâmetros da avaliação inicial, o eventual impacto da não participação sobre a incidência deve ser pequeno, isto é, a incidência em não participantes vivos seria provavelmente muito semelhante à dos incluídos no estudo.

6 CONCLUSÕES

Este estudo longitudinal, de base populacional, definiu a incidência de fratura vertebral, ajustada para sexo e idade, em população idosa brasileira. A incidência parece ser elevada, sendo mais frequente em mulheres, e com aumento da incidência com a idade. Foi confirmada a importância de alguns preditores de incidência em curto prazo de fraturas vertebrais, notavelmente idade, DMO e marcadores da remodelação óssea. Fatores de risco para fratura vertebral parecem ser diferentes de acordo com sexo. Esses resultados suportam a ideia de que, em termos de política de saúde pública, mais atenção deve ser dada aos esforços de prevenção de fraturas vertebrais a fim de melhorar o manejo da população idosa.

Anexo A - Aprovação do Comitê de Ética e do Departamento de Radiologia da Faculdade de Medicina da Universidade de São Paulo

APROVAÇÃO

A Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq da Diretoria Clínica do Hospital das Clínicas e da Faculdade de Medicina da Universidade de São Paulo, em sessão de 02/12/2009, **APROVOU** o Protocolo de Pesquisa nº **0825/09**, intitulado: **"INCIDÊNCIA DE FRATURAS VERTEBRAIS E FRATURAS CLÍNICAS NÃO VERTEBRAIS EM UMA POPULAÇÃO DE INDIVÍDUOS DE 65 ANOS OU MAIS."** apresentado pelo Departamento de **CLÍNICA MÉDICA**, inclusive o Termo de Consentimento Livre e Esclarecido.

Cabe ao pesquisador elaborar e apresentar à CAPPesq, os relatórios parciais e final sobre a pesquisa (Resolução do Conselho Nacional de Saúde nº 196, de 10/10/1996, inciso IX.2, letra "c").

Pesquisador (a) Responsável: **Rosa Maria Rodrigues Pereira**

Pesquisador (a) Executante: **Diogo Souza Domiciano**

CAPPesq, 03 de Dezembro de 2009

Prof. Dr. Eduardo Massad
Presidente da Comissão de
Ética para Análise de Projetos
de Pesquisa

Comissão de Ética para Análise de Projetos de Pesquisa do HCFMUSP e da FMUSP Diretoria Clínica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo Rua Ovídio Pires de Campos, 225, 5º andar - CEP 05403 010 - São Paulo - SP Fone: 011 3069 6442 Fax: 011 3069 6492 e-mail: cappesq@hcnet.usp.br / secretariacappesq2@hcnet.usp.br

DR APROVAÇÃO 29/2009

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APROVAÇÃO

O Conselho do Departamento de Radiologia aprovou "ad referendum" em 17.07.2009 o projeto de pesquisa:

Título: *Incidência de osteoporose, fraturas vertebrais e não vertebrais em uma população de indivíduos de 65 anos ou mais.*

Pesquisadora responsável: Dra. Rosa Maria Rodrigues Pereira

Pesquisadora executante: Diogo Souza Domiciano

Responsável pelo acompanhamento: Dr. André Scatigno Neto

RESSALVA

Interessado deverá entrar em contato com o Dr. André Scatigno Neto para acordo sobre a realização dos exames/procedimentos.

São Paulo, 17 de julho de 2009.

Prof. Dr. Roger Chammas
Chefe do Departamento de Radiologia
FMUSP

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APÊNDICES

Apêndice A - Artigo principal

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ORIGINAL ARTICLE

Incidence and risk factors for osteoporotic vertebral fracture in low-income community-dwelling elderly: a population-based prospective cohort study in Brazil. The São Paulo Ageing & Health (SPAH) Study

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Abstract

Summary We ascertained the incidence and predictors of radiographic vertebral fracture in a Brazilian elderly cohort, since no data in this field have been reported in low-income countries. This is the first population-based study to demonstrate the high frequency of vertebral fracture in elderly Latin Americans. Age, prior fracture, BMD, and bone turnover were predictors of fracture.

Introduction Vertebral fractures are associated with increased future fracture risk and mortality. No data on incidence of osteoporotic vertebral fracture have been reported in low-income countries where the population's aging has been faster. Thus, we sought to describe the incidence and risk factors for radiographic vertebral fracture in a longitudinal prospective Brazilian population-based elderly cohort.

Methods 707 older adults (449 women and 258 men) were evaluated with spinal radiographs obtained at baseline and after a mean follow-up of 4.3 ± 0.8 years. New vertebral fracture was defined as distinct alteration in the morphology of vertebrae resulting in higher grade of deformity on the second

radiograph when compared to the baseline radiograph. Clinical questionnaire, bone mineral density (BMD), and laboratory tests were performed at baseline. Multivariate Poisson regression models were used to identify independent predictors of fracture.

Results The age-standardized incidence of vertebral fracture was 40.3/1,000 person-years in women and 30.6/1,000 in men. In women, three models of risk factors for fracture were fitted: (1) age (relative risks (RR) 2.46, 95 % confidence interval (CI) 1.66–3.65), previous osteoporotic fracture (RR 1.65, 95 % CI 1.00–2.71), and lumbar spine BMD (RR 1.21, 95 % CI 1.03–1.41); (2) age (RR 2.25, 95 % CI 1.52–3.34) and femoral neck BMD (RR 1.42, 95 % CI 1.11–1.81); (3) age (RR 2.11, 95 % CI 1.41–3.15) and total hip BMD (RR 1.56, 95 % CI 1.21–2.0). In men, the highest quartile of cross-linked C-telopeptide (CTX) (RR 1.96, 95 % CI 0.98–3.91) and prior fracture (RR 2.10, 95 % CI 1.00–4.39) were predictors of new vertebral fracture.

Conclusions This is the first population-based study to ascertain the incidence of vertebral fracture in elderly Latin Americans, confirming the high frequency of the disorder. Age, prior fracture, BMD, and bone turnover were predictors of the short-term incidence of vertebral fracture.

Keywords Aging · Incidence · Osteoporosis · Risk factors · Vertebral fracture

Introduction

Globally, aging impacts all countries, particularly underdeveloped nations [1]. Currently, 65 % of elderly persons reside in less-developed countries, and this rate is projected to increase

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to almost 80 % by 2050 [2]. Brazil is a low-/middle-income country undergoing a marked socio-demographic transition, with one of the fastest aging populations in the world [3]. Older Brazilian adults have lived through marked socioeconomic changes that rapidly transformed the country from a rural agrarian society into a diversified urban one [1, 3]. Many older adults who live in urban centers represent those who survived high infant mortality and endured significant socioeconomic adversity throughout their lives. This Brazilian demographic transition is part of a worldwide process that has been occurring in low-income countries in Latin America, Africa, and Asia [1].

With aging populations and increasing life expectancies, low-income countries will inevitably see changes in chronic disease burdens, such as osteoporotic fractures. Furthermore, women constitute an increasingly larger portion of an aging population [4]. This phenomenon reinforces the concern about the burden of vertebral fracture, which is the most common osteoporotic fracture [5], affecting 20 % of postmenopausal women [6].

Only 25–30 % of vertebral fractures cause symptoms and receive clinical attention [5]. However, even asymptomatic vertebral fractures are associated with adverse outcomes [7, 8], including increased mortality [9, 10].

The incidence of vertebral fracture assessed in prospective cohort studies is relevant for comparing the burden of osteoporotic fractures between populations. However, all prospective data on incidence of vertebral fracture have come from developed countries [11–13]. No prospective survey has evaluated the incidence and predictors of vertebral fracture in low-income countries.

Thus, the present study aimed to determine the incidence of and risk factors for radiographically assessed osteoporotic vertebral fracture in a prospective Brazilian population-based elderly cohort.

Materials and methods

Subjects

From June 2005 to July 2007, a total of 1,025 older subjects were enrolled in the São Paulo Ageing & Health (SPAH) Study, a prevalence survey of osteoporotic fractures. Details about the methodology have been described elsewhere [14]. Briefly, the SPAH recruited all residents ≥ 65 years from 66 census areas in the Butantã district, an urban neighborhood located in the city of São Paulo (located in the south of Brazil). During the first stages of the study, all older adults living in the district were identified through census records. This sample was similar in age, sex, and social class characteristics to the entire Brazilian elderly population [4]. Only well-functioning

elderly men and women were recruited to participate in this study.

Between 2010 and 2012, all subjects were re-invited to participate in a second evaluation (the incidence analysis). Individuals were recruited by telephone calls and door-to-door visits. They were brought from their homes to the research center via a shuttle service specifically hired for the study. Of those who did not return for the second evaluation, 132 (12.9 %) individuals had died and 168 (16.4 %) could not be contacted because they were living outside of São Paulo (loss of follow-up). Mortality data were confirmed by death certificates obtained from the publicly available databases of the *Improvement Program of Information on Mortality in São Paulo* (PRO-AIM) Foundation, which is the institute responsible for vital statistics in São Paulo.

Of the 1,025 first-phase participants, 725 subjects agreed to take part in the second evaluation (response rate in surviving subjects, 81.2 %). Eighteen (1.8 %) individuals were excluded due to lack of some baseline laboratory or bone mineral density (BMD) data, or due to cancer, a condition that has been positively associated with pathological fractures. In total, 707 subjects (69.0 % of the original cohort) were included in the present study (Fig. 1).

This study was approved by the Local Ethics Committee, and all participants gave written informed consent.

Definition of incident fractures

Baseline and follow-up vertebral fractures were evaluated by lateral thoracic/lumbar spine radiographs. All radiographic images were analyzed by two rheumatologists who were experienced in vertebral fracture assessment. The readers evaluated each T4–L4 vertebrae image using a semi-quantitative (SQ) method [15]. The reliability between readers was analyzed using 60 X-ray images; inter-observer agreement was 96 %, and the kappa coefficient was 0.83.

On baseline and follow-up radiographs, each identified vertebral fracture was classified by grade based on the SQ scale: mild (grade 1)—reduction of 20–25 % of anterior, middle, and/or posterior height relative to the adjacent vertebral bodies; moderate (grade 2)—reduction of 26–40 %; or severe (grade 3)—reduction >40 %. When a vertebral fracture was detected in the follow-up X-ray, the baseline radiograph was also analyzed, and if the fracture was already present, it was considered to be a baseline fracture. In this way, a new fracture was defined if the vertebra was determined to be normal at baseline and if any of the three vertebral heights (anterior, central, or posterior) showed a decrease of at least 20 % in absolute height on the later film. A new fracture was also defined if there was a worsening of the grade of the baseline fracture (grade 1 to 2 or 3, grade 2 to 3) in the second radiograph.

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Fig. 1 São Paulo Ageing & Health (SPAH) Study population

Fracture risk factors

The potential predictors of incident vertebral fracture were investigated using baseline information including clinical characteristics, laboratory tests, and BMD.

Baseline clinical variables

At baseline, information was obtained by a standardized questionnaire administered in person. The form included questions on age, dairy product consumption, smoking status, alcohol consumption, menopause age, physical activity, previous non-vertebral fracture, hip fracture in first-degree relatives, falls during the last year, comorbidities, and current medication(s) [14]. Individuals were asked to bring all medications to the baseline clinic visit.

Height, weight, and body mass index (BMI) of each participant were measured using standard protocols.

Baseline laboratory variables

The serum concentration of 25-hydroxy vitamin D (25OHD) was measured using the radioimmunoassay technique (DiaSorin, Stillwater, MN, USA), and intact parathyroid hormone (iPTH) was measured by immunoradiometric assay (ELSA-PTH, CIS Bio International, France) [14].

Serum bone turnover markers, amino-terminal propeptide of type I procollagen (P1NP), and cross-linked C-telopeptide

(CTx) were analyzed by an automated Roche electrochemiluminescence system (E411, Roche Diagnostics®, Mannheim, Germany). The coefficients of variation for P1NP and CTx were 2.2 and 2.5 %, respectively.

Baseline bone mineral density

BMD at lumbar spine, femoral neck, and total hip was measured by Hologic QDR 4500A densitometry (DXA) equipment (Hologic Inc. Bedford, MA, USA, Discovery model) [14].

Statistical analysis

Incidence

Survival time (in months) for each subject was measured as the interval between baseline examination date and the date of the second spinal radiograph. Incidence was expressed as the number of individuals with at least one incident fracture per 1,000 person-years (pyr) at risk, stratified by sex and 10-year age band. In addition, 95 % confidence intervals (CIs) were calculated using the exact Poisson formula. Results are shown separately for men and women as crude incidence rates and standardized to the Brazilian elderly population in the year 2010 [4]. Relative risks (RR) and 95 % CIs were used to compare the fracture incidence rates of men and women.

Risk factors

Continuous variables were expressed as means±standard deviations (SDs) and categorical variables as counts and percentages. The chi-square test, Fisher's test, likelihood ratio test, unpaired Student's *t* test or Mann–Whitney's test were used to compare differences in baseline characteristics between individuals with and without incident fracture, separately for each sex. All risk factors associated with new vertebral fractures with *p* value <0.10 (two-tailed test) in the univariate analysis were included in multivariate regression models. Multivariate Poisson regression models were constructed to identify independent predictors of fracture and to derive continuous hazard functions. The outcome was the estimated risk of any grade of vertebral fracture. Results were reported as relative risks (RRs) with 95 % CIs.

Non-participation analysis

Of 1,025 attendees in the original cohort, 707 were included in the follow-up phase. To evaluate the potential impact of non-participation on the observed incidence rate, we assessed the differences in baseline characteristics between participants (*N*=707) and non-participants (*N*=318), assuming that the relationship between baseline risk factors and subsequent fracture was the same in both groups [12]. To rule out the possibility that those most at risk for fractures might have died, we also performed the non-participation analysis excluding the 132 individuals who died during the study period.

STATA, version 11.0, was used to calculate the incidence rates. Estimates of the incidence rate ratio and 95 % CI were generated by SPSS, version 20.0.

Results*Characteristics of the study cohort*

A total of 707 subjects (449 women, 258 men) ≥65 years were included in the cohort. The average monthly household income was US\$459.61±356.05 (R\$1,098.48±850.96), and 261 (36.9 %) had a monthly household income equivalent to the minimum wage (currently US\$302.93 or R\$724.00). The mean time in school was 2.9 years, 206 (29.2 %) had spent from 1 to 3 years in school, and 218 (30.8 %) were illiterate.

Due to variations in scheduling of the second survey, the period between baseline and the second assessment varied among participants (follow-up time 4.3±0.8 years, range 2.2–6.5 years).

Incidence rates

Seventy-seven (17.1 %) women and 34 (13.2 %) men had incident vertebral fractures. Altogether, 63 (11.2 %) subjects experienced a single fracture during the study period, 32 had two fractures, 10 had three, 3 had four, and 1 individual had five, six, or seven fractures each. The incidence rates by sex and age are shown in Table 1 and Fig. 2. The crude incidence of vertebral fracture was 40.3/1,000 pyr in women and 30.6/1,000 pyr in men. The incidence rates after age-standardization to the Brazilian older population (≥65 years) were 44.0/1,000 pyr in women and 32.6/1,000 pyr in men. In both sexes, the incidence increased markedly in older age groups (≥80 years). The fracture rate was significantly higher in women than in men both between the ages of 70–79 years (33.1/1,000 and 22.4/1,000 pyr, respectively) and at 80 years or older (97.5/1,000 and 57.9/1,000 pyr), but slightly less for those aged 65–69 years (35.3/1,000 pyr in women and 36.5/1,000 pyr in men) (Table 1 and Fig. 2). The overall female:male vertebral fracture risk ratio was 1.21, but this ratio increased with age (Table 1).

Thirty-four (7.6 %) women and 14 (5.4 %) men had moderate/severe vertebral fracture. The crude incidence rates were 17.8/1,000 pyr in women and 12.6/1,000 pyr in men.

Independent risk factors for new vertebral fracture

Baseline characteristics stratified by fracture status and sex are presented in Tables 2 and 3. Univariate analyses showed that women with at least one incident vertebral fracture compared to those with none were older, more frequently white, shorter, had lower weight, lower BMI, and an increased time since menopause. These women also had a higher prevalence of any osteoporotic fracture, lower estimated glomerular filtration rate (eGFR), higher CTx, and lower BMD at lumbar spine, femoral neck, and total hip.

Men with new fractures tended to be heavier drinkers and to have higher prevalence of osteoporotic fracture and higher values of CTx compared to those without incident fractures.

In women, Poisson regression revealed three possible models of independent predictors of vertebral fracture, after adjustment for other variables: (1) age (RR 2.46, 95 % CI 1.66–3.65, *p*<0.001, per 10-year increase), previous osteoporotic fracture (RR 1.65, 95 % CI 1.00–2.71, *p*=0.049), and lumbar spine BMD (RR 1.21, 95 % CI 1.03–1.41, *p*=0.017, per 1 SD decrease); (2) age (RR 2.25, 95 % CI 1.52–3.34, *p*<0.001) and femoral neck BMD (RR 1.42, 95 % CI 1.11–1.81, *p*=0.006); and (3) age (RR 2.11, 95 % CI 1.41–3.15, *p*<0.001) and total hip BMD (RR 1.56, 95 % CI 1.21–2.01, *p*=0.001) (Fig. 3).

Although the risk ratios were only borderline significant, the highest quartile of CTx (RR 1.96, 95 % CI 0.98–3.91, *p*=0.057) and prior osteoporotic fracture (RR 2.10, 95 % CI

Table 1 Incidence of radiographic vertebral fractures by age and sex

Age (years)	Women				Men				Relative risk female:male [95 % CI]
	Subjects (n)	Person years at risk	Subjects with fracture (n)	Incidence (/1,000) [95 % CI]	Subjects (n)	Person years at risk	Subjects with fracture (n)	Incidence (/1,000) [95 % CI]	
65–69	130	538	19	35.3 [22.4–55.4]	90	384	14	36.5 [21.6–61.6]	1.08 [0.54–2.15]
70–79	275	1,178	39	33.1 [24.2–45.3]	143	625	14	22.4 [13.3–37.8]	1.38 [0.75–2.55]
≥ 80	44	195	19	97.5 [62.2–152.8]	25	104	6	57.9 [26.0–128.8]	0.97 [0.37–2.53]
All	449	1,910	77	40.3 [32.2–50.4]	258	1,113	34	30.6 [21.8–42.8]	1.21 [0.80–1.81]

1.00–4.39, $p=0.050$) were independent predictors of new fracture in men, after adjustment for other significant variables from the univariate analyses plus age, BMI, eGFR, and BMD (Fig. 3).

Non-participation

Compared to participants, women who were not present for the second evaluation were older (74.9 ± 6.6 vs. 72.9 ± 4.8 years, $p < 0.001$), had a lower BMI (28.1 ± 5.4 vs. 29.1 ± 5.3 kg/m², $p = 0.035$), were less physically active (22.2 vs. 4.7 %, $p < 0.001$), and had a higher prevalence of diabetes mellitus (29.0 vs. 20.0 %, $p = 0.017$). Non-participant women also had a lower frequency of anti-fracture medication use (0.6 vs. 6.9 %, $p = 0.001$), a lower eGFR (54.7 ± 19.0 vs. 59.5 ± 19.0 mL/min/1.73 m², $p = 0.007$), a higher iPTH (48.3 ± 34.8 vs. 40.6 ± 17.3 pg/mL, $p = 0.041$), and a lower 25OHD level (16.9 ± 8.5 vs. 18.9 ± 9.1 ng/mL, $p = 0.011$). For men, the comparison revealed that non-participants were older (73.6 ± 5.6 vs. 72.3 ± 4.7 years, $p = 0.023$), were more likely to be white (76.1 vs. 64.3 %, $p = 0.020$), were more likely to suffer from recurrent falls (15.5 vs. 7.0 %, $p = 0.007$) or

be less physically active (19.7 vs. 9.3 %, $p = 0.011$), and to have lower 25OHD levels (19.8 ± 10.1 vs. 22.2 ± 9.3 ng/mL, $p = 0.018$). Non-participant men also had a higher CTx (0.425 ± 0.261 vs. 0.342 ± 0.201 ng/mL, $p = 0.010$) and lower total hip BMD (0.903 ± 0.166 vs. 0.935 ± 0.137 g/cm², $p = 0.043$). However, when deceased non-participants were excluded, most differences became non-significant (Table 4).

Discussion

To the best of our knowledge, this is the first population-based study to determine the incidence of vertebral fracture in a Latin American cohort. In a Brazilian community-dwelling older population followed for an average of 4.3 years, we showed that 17 % of women and 13 % of men presented with new radiographic vertebral fractures.

The SPAH is a longitudinal population-based study with several strengths, including a high participation rate and a homogeneous and well-characterized community-dwelling

Fig. 2 Incidence of radiographic vertebral fractures by age and sex

Table 2 Baseline clinical features of subjects with and without incident vertebral fracture

Baseline characteristics	Women		<i>p</i> ^a	Men		<i>p</i> ^a
	Fracture (<i>n</i> =77)	No fracture (<i>n</i> =372)		Fracture (<i>n</i> =34)	No fracture (<i>n</i> =224)	
Age—years	75.4 (6.3)	72.4 (4.2)	<0.001	73.3 (5.9)	72.2 (4.4)	0.293
Race— <i>n</i> (%)						
White	56 (19.8)	227 (80.2)	0.053	23 (13.9)	143 (86.1)	0.666
Non-white	21 (12.7)	145 (87.3)		11 (12.0)	81 (88.0)	
Height—cm	149.1 (6.5)	150.5 (5.9)	0.060	163.2 (9.3)	162.5 (7.2)	0.696
Weight—kg	60.8 (12.7)	66.8 (13.3)	<0.001	69.9 (11.2)	70.6 (12.4)	0.741
BMI—kg/m ²	27.3 (5.2)	29.4 (5.3)	0.001	26.2 (3.4)	26.7 (4.2)	0.508
Years since menopause	27.3 (6.9)	23.6 (6.8)	<0.001	NA	NA	
Current estrogen user— <i>n</i> (%)	6 (18.2)	27 (81.8)	0.870	NA	NA	
Smoking— <i>n</i> (%)						
Current	9 (18.8)	39 (81.2)	0.935	3 (9.4)	29 (90.6)	0.589
Past	18 (16.4)	92 (83.6)		20 (15.2)	112 (84.8)	
Never	50 (17.2)	241 (82.8)		11 (11.7)	83 (88.3)	
Alcohol use (≥3 units/day)— <i>n</i> (%)	0 (0)	2 (100.0)	>0.999	4 (28.6)	10 (71.4)	0.096
Chronic faller (≥2 falls/year)— <i>n</i> (%)	17 (23.3)	56 (76.7)	0.128	2 (11.1)	16 (88.9)	>0.999
Physical activity score— <i>n</i> (%)						
Low	6 (28.6)	15 (71.4)	0.139	3 (12.5)	21 (87.5)	0.389
Moderate	55 (18.3)	246 (81.7)		20 (11.4)	155 (88.6)	
High	16 (12.6)	111 (87.4)		11 (18.6)	48 (81.4)	
Parental history of fracture— <i>n</i> (%)	6 (12.8)	41 (87.2)	0.302	2 (13.3)	13 (86.7)	0.942
Dairy product intake—mg/day	414.6 (281.0)	470.6 (308.6)	0.142	343.9 (225.7)	403.0 (319.5)	0.300
Diabetes mellitus— <i>n</i> (%)	13 (14.4)	77 (85.6)	0.446	3 (7.7)	36 (92.3)	0.272
Other comorbidities ^b — <i>n</i> (%)	4 (15.4)	22 (84.6)	>0.999	1 (11.1)	8 (88.9)	>0.999
Any prior osteoporotic fracture ^c — <i>n</i> (%)	23 (23.5)	75 (76.5)	0.060	10 (22.7)	34 (77.3)	0.040
Prior moderate/severe vertebral fracture— <i>n</i> (%)	15 (23.1)	50 (76.9)	0.170	6 (19.4)	25 (80.6)	0.266
Prior non-vertebral fracture— <i>n</i> (%)	11 (25.6)	32 (74.4)	0.123	5 (31.2)	11 (68.8)	0.044
Current calcium supplements user— <i>n</i> (%)	10 (25)	30 (75)	0.168	0 (0)	1 (100)	>0.999
Current vitamin D supplements user— <i>n</i> (%)	6 (28.6)	15 (71.4)	0.229	0 (0)	2 (0)	>0.999
Current bisphosphonate user— <i>n</i> (%)	7 (25.9)	20 (74.1)	0.162	0 (0)	1 (100.0)	>0.999

Categorical variables were expressed as *n* (%) and continuous variables as mean (1 SD)

BMI body mass index, NA not applicable

^a*p* values are for comparison of means (Student's *t* test or Mann-Whitney's test) or proportions (chi-square test, Fisher's test, or likelihood ratio test)^bHyperthyroidism, primary hyperparathyroidism, asthma/chronic obstructive pulmonary disease, chronic hepatic disease, hypertension, previous stroke, and myocardial infarction^cIncluding non-vertebral plus moderate/severe vertebral fractures

sample which is likely representative of the Brazilian elderly population [4]. Moreover, vertebral fractures were diagnosed by radiograph to ensure complete ascertainment (only approximately 30 % of such fractures are symptomatic) [5]. We applied a semi-quantitative methodology, which has been recommended for use in clinical practice to score fracture severity [16]. Unlike studies utilizing hospital discharge surveys [5, 17], we employed rigorous protocols based on a comparison of two successive radiographs to define incident fracture, which reduced the possibility of a false-positive diagnosis. Finally, we investigated a more comprehensive set of risk factors than those previously

examined by other cohorts, including laboratory and BMD parameters [18–20].

Overall, the incidence rate of vertebral fractures in Brazilian elderly people was 1.5–6 times higher than that observed in European countries, including Scandinavia (which has the highest rates in Europe) [12]. However, any comparison with other studies is hampered by a lack of consensus on the definition of fracture [21, 22].

Conversely, the annual incidence rates reported here were broadly similar to those found in Asian populations [23, 24], notably in Japan, where the annual incidence rate for women in their 70s was 40/1,000 and 84/1,000 pyr for women in their

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Table 3 Baseline laboratorial parameters and BMD measurements of subjects with and without incident vertebral fracture

Baseline characteristics	Women		p^a	Men		p^a
	Fracture ($n=77$)	No fracture ($n=372$)		Fracture ($n=34$)	No fracture ($n=224$)	
eGFR—mL/min/1.73 m ²	50.7 (16.8)	61.3 (18.9)	<0.001	57.0 (17.2)	60.5 (17.0)	0.300
iPTH—pg/mL	43.2 (20.1)	40.0 (16.6)	0.144	39.0 (20.0)	36.2 (16.3)	0.400
25OHD categories— n (%)						
<20 ng/mL	42 (15.8) ^b	224 (84.2) ^c	0.569	17 (13.9) ^d	105 (86.1) ^e	0.729
21–29 ng/mL	27 (19.9) ^b	109 (80.1) ^c		2 (13.5) ^d	77 (86.5) ^e	
>30 ng/mL	7 (15.6) ^b	38 (84.4) ^c		4 (9.3) ^d	39 (90.7) ^e	
25OHD—ng/mL	19.4 (9.4)	18.8 (9.0)	0.578	20.5 (9.6)	22.4 (9.2)	0.300
CTx quartiles— n (%)						
Q1–Q3	52 (15.6)	282 (84.4) ^f	0.093	21 (11.1) ^g	169 (88.9) ^h	0.047
Q4 ^k	25 (22.5)	86 (77.5) ^f		13 (21.0) ^g	49 (79.0) ^h	
CTx—ng/mL	0.447 (0.241)	0.408 (0.238)	0.184	0.389 (0.180)	0.335 (0.203)	0.149
PINP quartiles— n (%)						
Q1–Q3	53 (15.8)	283 (84.2) ⁱ	0.157	23 (12.0)	169 (88.0) ^j	0.267
Q4 ^l	24 (21.6)	87 (78.4) ⁱ		11 (17.5)	52 (82.5) ^j	
PINP—ng/mL	46.55 (26.04)	44.19 (29.59)	0.516	44.82 (24.32)	39.25 (21.55)	0.169
BMD status— n (%)						
Normal	6 (14.3)	36 (85.7)	0.099	5 (11.4)	39 (88.6)	0.351
Osteopenia	19 (12.4)	134 (87.6)		22 (15.9)	116 (84.1)	
Osteoporosis	52 (20.5)	202 (79.5)		7 (9.2)	69 (90.8)	
Lumbar spine BMD—g/cm ²	0.773 (0.158)	0.834 (0.172)	0.004	0.993 (0.187)	1.009 (0.188)	0.654
Femoral neck BMD—g/cm ²	0.607 (0.114)	0.666 (0.123)	<0.001	0.731 (0.093)	0.751 (0.136)	0.280
Total hip BMD—g/cm ²	0.722 (0.120)	0.804 (0.131)	<0.001	0.912 (0.117)	0.938 (0.140)	0.309

Categorical variables were expressed as n (%) and continuous variables as mean (1 SD)

eGFR estimated glomerular filtration rate, iPTH intact parathyroid hormone, 25OHD 25-hydroxy vitamin D, CTx type I collagen C-telopeptide, PINP N-terminal propeptide of type I collagen, Q quartile, BMD bone mineral density

^a p values are for comparison of means (Student's t test or Mann–Whitney's test) or proportions (chi-square test, Fisher's test, or likelihood ratio test)^b $n=76$ ^c $n=371$ ^d $n=33$ ^e $n=221$ ^f $n=368$ ^g $n=34$ ^h $n=218$ ⁱ $n=370$ ^j $n=221$ ^k >0.529 ng/mL in women and >0.440 ng/mL in men^l >55.49 ng/mL in women and >47.09 ng/mL in men

80s. Notably, the Japanese study and the present one used the same methodology (SQ) and had similar follow-up times [13]. In contrast to morphometric approach, which is subject to measurement error in terms of point placement (at the borders of the vertebra), SQ approach has greater sensitivity to identify vertebral fractures. This discrepancy seems to be greatly due to the presence of minor vertebral deformities which do not fulfill the morphometric criteria but are classified as grade 1 fractures by SQ method [25]. Of note, a recent meta-analysis of control arms of four anti-osteoporotic trials showed that the

presence of mild vertebral fractures was associated with an increased risk of future vertebral fracture [26].

As previously described for hip fractures, it is possible that there are genuine differences in occurrence of vertebral fractures between this study's population and other groups that are related to Brazil's very large size as well as its substantial ethnic admixture and distinct lifestyle habits [27–29]. Nonetheless, in São Paulo, where there are a mixture of Europeans (White Portuguese and Italians), native Brazilians, Japanese descendants, as well as many individuals

Fig. 3 Risk factors predictive of new vertebral fractures women and men, with the relative risk (RR) of each variable according the multivariate models

who were born in other parts of the country, the population seems to be more representative of Brazilian ethnic miscegenation.

Country-specific absolute risk algorithms (FRAX®) recently have been developed to predict the 10-year probability of fracture. However, the FRAX® models for some countries, including Brazil, are based only on hip fracture risk due to the lack of ethnic-specific data for other fracture types and use assumptions (i.e., the ratio of hip-to-vertebral fracture observed from the Swedish population) to derive the relevant risk functions for other major fractures including vertebral fractures [30]. However, the Swedish ratio of hip-to-vertebral fracture was based on incidence rates only of clinically apparent vertebral fractures, not including asymptomatic

fractures diagnosed radiographically. In addition, the spine-to-hip fracture ratio varies between countries; for instance, Asians have a much higher spine-to-hip fracture ratio (1.7–6.3) than Caucasians (0.5–1.4) [23]. Finally, we found a higher vertebral-to-hip ratio (1.8–2.8) in older Brazilian adults, which suggests that a FRAX model that assumes a Swedish ratio of vertebral-to-hip fracture might underestimate the absolute risk of major osteoporotic fracture.

In Brazil, cross-sectional studies have reported risk factors for prevalent osteoporotic fracture [14, 31], but the present survey is the first longitudinal population-based study to determine the predictors of incident radiographic vertebral fracture in the Brazilian population. In women, age and BMD were the strongest predictors of vertebral fracture.

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Table 4 Characteristics of participants and non-participants (excluding deceased subjects) in the prospective phase of the SPAH study

Baseline characteristics	Participation		<i>p</i> ^a			<i>p</i> ^a
	Women			Men		
	Yes (<i>n</i> =449)	No (<i>n</i> =109)		Yes (<i>n</i> =258)	No (<i>n</i> =77)	
Age—years	72.9 (4.8)	73.7 (5.9)	0.156	72.3 (4.7)	71.8 (4.1)	0.401
White race— <i>n</i> (%)	283 (63.0)	73 (67.0)	0.053	166 (64.3)	60 (77.9)	0.010
BMI—kg/m ²	29.1 (5.3)	29.1 (5.1)	0.980	26.6 (4.1)	26.3 (4.1)	0.584
Smoking— <i>n</i> (%)						
Current	48 (10.7)	11 (10.0)	0.580	32 (12.4)	14 (18.2)	0.420
Past	110 (24.5)	32 (29.4)		132 (51.2)	38 (49.3)	
Never	291 (64.8)	66 (60.6)		94 (36.4)	25 (32.5)	
Alcohol use (≥3 units/day)— <i>n</i> (%)	2 (0.5)	0	>0.999	14 (5.4)	6 (7.8)	0.620
Chronic faller (≥2 falls/year)— <i>n</i> (%)	73 (16.3)	17 (15.6)	0.866	18 (7.0)	8 (10.4)	0.326
Physical activity score— <i>n</i> (%)						
Low	21 (4.7)	18 (16.5)	<0.001	24 (9.3)	10 (13.0)	0.213
Moderate	301 (67.0)	73 (67.0)		175 (67.8)	56 (72.7)	
High	127 (28.3)	18 (16.5)		59 (22.9)	11 (14.3)	
Parental history of fracture— <i>n</i> (%)	47 (10.5)	9 (8.3)	0.337	15 (5.8)	7 (9.1)	0.587
Dairy product intake—mg/day	460.9 (304.5)	414.3 (274.5)	0.144	395.2 (309.1)	417.4 (366.9)	0.600
Diabetes mellitus— <i>n</i> (%)	90 (20.0)	26 (23.9)	0.385	39 (15.1)	9 (11.7)	0.437
Prior non-vertebral fracture— <i>n</i> (%)	43 (9.6)	11 (10.1)	0.870	16 (6.2)	6 (7.8)	0.621
Prior moderate/severe vertebral fracture— <i>n</i> (%)	119 (26.5)	24 (22.0)	0.336	74 (28.7)	23 (29.9)	0.840
Current anti-fracture medication—(%) ^b	31 (6.9)	0	0.005	1 (0.4)	0	>0.999
eGFR—mL/min/1.73 m ²	59.5 (19.0)	56.7 (17.4)	0.288	60.0 (17.0)	59.6 (15.7)	0.759
iPTH—pg/mL	40.6 (17.3)	44.1 (33.2)	0.864	36.6 (16.8)	40.1 (24.1)	0.471
25OHD—ng/mL	18.9 (9.1) ^c	17.0 (7.4)	0.024	22.2 (9.3) ^d	20.2 (9.7)	0.110
BMD status— <i>n</i> (%)						
Normal	42 (9.4)	14 (12.8)	0.457	44 (17.1)	18 (23.4)	0.350
Osteopenia	153 (34.1)	56 (51.4)		138 (53.5)	24 (31.2)	
Osteoporosis	254 (56.6)	39 (35.8)		76 (29.5)	35 (45.5)	
Lumbar spine BMD—g/cm ²	0.824 (0.171)	0.867 (0.198)	0.023	1.006 (0.188)	1.012 (0.213)	0.830
Femoral neck BMD—g/cm ²	0.656 (0.123)	0.671 (0.125)	0.266	0.749 (0.131)	0.762 (0.168)	0.528
Total hip BMD—g/cm ²	0.790 (0.133)	0.796 (0.138)	0.676	0.935 (0.137)	0.934 (0.162)	0.987

Categorical variables were expressed as *n* (%) and continuous variables as mean (1 SD)

BMI body mass index, eGFR estimated glomerular filtration rate, iPTH intact parathyroid hormone, 25OHD 25-hydroxy vitamin D

^a*p* values are for comparison of means (Student's *t* test or Mann-Whitney's test) or proportions (chi-square test, Fisher's test, or likelihood ratio test)^bIncluding calcium supplements, vitamin D supplements, bisphosphonates, or estrogen^c*n*=447^d*n*=240

Reproductive factors were not linked to increased vertebral fracture risk. Although time since menopause was associated with new fractures in the univariate analysis, it did not remain in the multivariate model after adjustment for age. In line with this finding, menopause status was not associated with increased vertebral fracture risk in American white women aged over 65 years [19]. These results might be explained by the advanced age of the studied population, which overlaps with the time since menopause and becomes a strongest risk factor after adjustment in the multivariate analysis. Furthermore,

other baseline features, including laboratory measurements such as renal function (eGFR), were univariately associated with new fractures in women but did not remain significant after adjustment for age and BMD.

In agreement with prior surveys [20, 32, 33], risk factors for vertebral fracture in men were less well characterized in this study. This outcome could be because vertebrae with mild height reduction represent a mixture of mild osteoporotic and degenerative deformities [34]. Alternatively, it may be that the small number of fractures observed in men reduced the study's

statistical power to detect the association of some risk factors with fractures. Moreover, SPAH study included only well-functioning older subjects, many of whom still held jobs that required physical exertion; thus, we could not rule out the possibility that some incident deformities may be related to occupational activities involving trauma, as previously reported [14, 35, 36].

Bone turnover has been reported to predict independent fracture risk [37–40]. However, few studies have been designed to investigate vertebral fracture [37–39] and have included men [40]. We found that men with higher levels of a bone resorption marker had a greater risk of vertebral fracture.

One of the main concerns is that potential differences in the risk of fracture between participants and non-participants of the second evaluation could over- or underestimate the true incidence of fracture. However, these differences became non-significant when deceased people were excluded, suggesting that those most at risk may have died and thus were not eligible to attend follow-up at all. In fact, age and hip BMD were the main factors that explained the increased fracture risk, and these variables were not significantly different between participants and living non-participants.

In conclusion, this community-based study provided age- and sex-specific incidence rates for vertebral fracture in an older Brazilian population. The incidence seems to be high. Advancing age, declining BMD, previous fracture, and increased bone turnover were determinants of the short-term incidence of vertebral fracture. Altogether, these findings support the notion that, in terms of public health policy, more attention should be paid to efforts at preventing vertebral fractures in order to improve the management of low-income older populations.

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Apêndice B - Artigos relacionados

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ORIGINAL ARTICLE

Discriminating sarcopenia in community-dwelling older women with high frequency of overweight/obesity: the São Paulo Ageing & Health Study (SPAH)

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Abstract

Summary The criteria most used for the definition of sarcopenia, those based on the ratio between the appendicular skeletal muscle mass (ASM) and the square of the height (h^2) underestimate prevalence in overweight/obese people whereas another criteria consider ASM adjusted for total fat mass. We have shown that ASM adjusted for fat seems to be more appropriate for sarcopenia diagnosis.

Introduction Since the prevalence of overweight and obesity is a growing public health issue, the aim of this study was to evaluate the prevalence and risk factors associated with sarcopenia, based on these two criteria, among older women.

Methods Six hundred eleven community-dwelling women were evaluated by specific questionnaire including clinical data. Body composition and bone mineral density were evaluated by dual X-ray absorptiometry. Logistic regression models were used to identify factors independently related to sarcopenia by ASM/h^2 and ASM adjusted for total fat mass criteria.

Results The prevalence of overweight/obesity was high (74.3 %). The frequency of sarcopenia was lower using the criteria of ASM/h^2 (3.7 %) than ASM adjusted for fat (19.9 %) ($P < 0.0001$). We also note that less than 5 % (1/23) of sarcopenic

women, according to ASM/h^2 , had overweight/obesity, whereas 60 % (74/122) of sarcopenic women by ASM adjusted for fat had this complication. Using ASM/h^2 , the associated factors observed in regression models were femoral neck T-score ($OR = 1.90$; 95 % CI 1.06–3.41; $P = 0.03$) and current alcohol intake ($OR = 4.13$, 95 % CI 1.18–14.45, $P = 0.03$). In contrast, we have identified that creatinine ($OR = 0.21$; 95 % CI 0.07–0.63; $P = 0.005$) and the White race ($OR = 1.81$; 95 % CI 1.15–2.84; $P = 0.01$) showed a significant association with sarcopenia using ASM adjusted for fat.

Conclusions In women with overweight/obesity, ASM adjusted for fat seems to be the more appropriate criteria for sarcopenia diagnosis. This finding has relevant public health implications, considering the high prevalence of overweight/obesity in older women.

Keywords Appendicular muscle mass · Fat mass · Obesity · Prevalence · Sarcopenia · Women

Introduction

Sarcopenia is a syndrome characterised by a progressive loss of skeletal muscle mass, resulting in decreased muscle strength, impairment of physical and functional capacity and an increased risk of death. It is primarily linked to the ageing process, but may also be secondary to several causes (malnutrition, neurodegenerative diseases, muscle atrophy related to disuse and endocrine diseases). In most cases, the aetiology is multifactorial, and it is difficult to characterise one specific underlying cause for sarcopenia [1].

The diagnosis depends on the measurement of the individual skeletal muscle mass, particularly the appendicular skeletal muscle mass (ASM) evaluated by dual X-ray absorptiometry

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(DXA), which is the method officially recommended in clinical practice. There are several criteria for sarcopenia based on skeletal muscle mass measurement [2–5]. The most widely used is that proposed by Baumgartner et al., which defines sarcopenia as being present when the ratio between the ASM (in kilograms) and height squared (square metres)— ASM/h^2 —is at least two standard deviations below the normal mean of the reference group measured using DXA [2]. This classification criterion was associated with physical disability in a New Mexico population, but its extrapolation to other populations has resulted in low prevalence rates for sarcopenia, ranging from 3 to 16 % [6–8]. Obesity may account for these unexpected results, as it has been demonstrated that this criteria have the disadvantage to underestimate the prevalence in overweight/obese people [9]. In 2003, Newman et al. proposed another criterion based on ASM measurement adjusted for total fat mass, which seems to identify more individuals with sarcopenia, particularly in obese subjects [5].

This is a relevant issue because the prevalence of overweight and obesity is increasing among older age groups, not only in developed countries [10–13], but also in other parts of the world including the Brazilian population [14]. Therefore, the aim of this study was to evaluate the prevalence and risk factors associated with sarcopenia, according to these two criteria in community-dwelling older women.

Materials and methods

This study is an extension of the epidemiological project “Prevalence and risk factors of radiographic vertebral fracture in community-dwelling Brazilian elderly”, a population-based survey (São Paulo Ageing and Health Study—SPAH) [15]. This study was conducted from June 2005 to July 2009, involving individuals aged 65 years or over, in the district of Butantã, in the West Zone of São Paulo, Brazil. All of the individuals were clinically healthy and showed no evidence of malabsorption, chronic diarrhoea, hepatic disease, severe chronic diseases, or cancer. None of the subjects used anabolic steroids or protein supplements.

Clinical and radiographic evaluation

Out of the 959 individuals evaluated for the first study [15], 611 women were included in this protocol. All the individuals answered a standardised questionnaire regarding lifestyle and health, including family history of hip fracture, fragility and previous fractures, track record of falls during the last year, physical activity, current alcohol intake, current tobacco use, personal history of hypertension, diabetes mellitus, cardiovascular events (myocardial infarction and cerebrovascular disease), dietary calcium intake and age at menopause.

Previous fragility fractures were also analysed separately: non-vertebral and vertebral fractures. The personal history of non-vertebral fracture was determined in individuals who had fallen from standing height or less after 50 years of age with a fracture occurring at the most common sites of bone fragility (for example, rib, forearm, humerus and femur) [16]. Vertebral fractures were diagnosed from standard lateral thoracic and lumbar spine radiographs taken from all study participants using a 40-in tube-to-film distance centred on T7 and L2. Images of the T4–L4 vertebrae were evaluated by an expert skeletal radiologist using a Genant semiquantitative approach [17]. Only grade 2 and grade 3 fractures were included in the analysis.

Individuals who had two or more falls in the last 12 months were defined as chronic fallers [18]. An alcohol user was defined as anyone with a current intake of three or more units daily [19]. Physical activity was classified as: low—not even housework is performed; moderate—performs regular housework, occasionally walks, gardening; and high—performs regular physical activity apart from their daily routine at least twice a week for 30 min [20]. Calcium intake was evaluated by dairy product consumption like milk or yoghurt (millilitres per day) and cheese (grams per day) during the 7 days prior to the interview [21]. Race was defined based on the self-reported race of second generation ancestors, an approach previously used for the Brazilian population [22]. Individuals with four grandparents reported as White were classified as White, while those individuals with Black and White ancestors (mixed race) were classified as non-White. Individuals with Asian ancestors were also classified as non-White. When racial information regarding the grandparents was not available, an individual's race was determined by the race of his or her parents. The height (without shoes) of each participant was measured to the nearest 0.1 cm with a wall-mounted stadiometer. The weight of each participant (without shoes, wearing only light clothing) was measured to the nearest 0.25 kg using a double-beam balance scale.

Body mass index (BMI) was calculated by dividing the participants' weight (in kilograms) by their height squared (square metres). Individuals were classified by their BMI using both the classification used by the World Health Organisation (WHO) [23] and that recommended by Lipschitz [24]. The WHO cutoff points are: underweight ($BMI < 18.5 \text{ kg/m}^2$), normal weight ($BMI \geq 18.5$ and $< 25 \text{ kg/m}^2$), overweight or pre-obese ($BMI \geq 25$ and $< 30 \text{ kg/m}^2$), subject with class I obesity ($BMI \geq 30$ and $< 35 \text{ kg/m}^2$), subject with class II obesity ($BMI \geq 35$ and $< 40 \text{ kg/m}^2$), and subject with class III obesity ($BMI \geq 40 \text{ kg/m}^2$). In contrast, the classification proposed by Lipschitz considers the body composition changes from ageing, namely underweight ($BMI < 22 \text{ kg/m}^2$), normal weight ($BMI \geq 22$ and $\leq 27 \text{ kg/m}^2$) and overweight/obese

(BMI >27 kg/m²). This study was approved by the Local Ethics in Research Committee of the School of Medicine at the University of São Paulo (FM-USP), and all participants have given written informed consent.

Laboratory evaluation

The concentrations of serum calcium (adjusted for the albumin concentration), phosphorus, alkaline phosphatase, creatinine, total cholesterol, HDL, triglycerides, albumin and glucose were determined using standard automated laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault equation [25]. The concentration of serum 25-hydroxyvitamin D (25OHD) was measured using the radioimmunoassay technique (DiaSorin, Stillwater, MN, USA) with a lower detection limit of 5 ng/mL. Vitamin D was expressed by the mean (standard deviation) and also by vitamin D categories according to the definitions of 2011 Endocrine Society Clinical Practice Guideline [vitamin D deficiency as a 25OHD below 20 ng/mL (50 nmol/L), vitamin D insufficiency as a 25OHD of 21–29 ng/mL (52.5–72.5 nmol/L) and vitamin D sufficiency as a 25OHD ≥30 ng/mL (75 nmol/L)] [26].

The intra- and inter-assay variation coefficients in our laboratory were 10.5 and 17.8 %, respectively. Intact parathyroid hormone serum concentrations were measured by immunoradiometric assay (ELSA-PTH, CIS bio international, France), with reference variations of 11–65 pg/mL.

Body composition and bone mineral density

Body composition and bone mineral density (BMD) were determined by DXA, using Hologic QDR 4500A densitometry equipment (Hologic Inc. Bedford, MA, USA, Discovery model), at the following regions: lumbar spine, femoral neck, total femur and total body. All DXA measurements were performed by the same experienced technologist.

Appendicular lean mass was calculated as the sum of arms and legs lean soft tissue masses, assuming that all non-fat and non-bone tissue is skeletal muscle. The total body fat was expressed in grams and as a percentage of body weight.

The precision error for DXA measurements was determined based on standard ISCD protocols [27]. We calculated the least significant change with 95 % confidence to be 3.3 % for lumbar spine, 4.7 % for femoral neck, 3.9 % for total femur and 1 % for the whole body.

Definitions of sarcopenia

According to Baumgartner's criteria, sarcopenia is defined when the relative skeletal muscle mass index (RSMI=ASM/height²) is less than 5.45 kg/m² (value for female) [2].

The Newman's criteria is also based on ASM measurement adjusted for height (similar to Baumgartner's), but also for total fat mass [5]. Linear regression was used to model the association between ASM on height (in metre) and fat mass (in kilograms). The residuals from linear regression models were used to identify those individuals whose amount of ASM (obtained from DXA) was lower than expected (obtained by an equation resultant from the model) for a given amount of fat mass. A positive residual would indicate a relatively muscular individual, whereas negative values would indicate relatively sarcopenic individual. Our equation resultant from the model was:

$$\text{ASM}(\text{in kilograms}) = -14.51 + 17.27 \times \text{height}(\text{in metres}) + 0.20 \times \text{fat mass}(\text{in kilograms})$$

The 20th percentile was defined as the cutoff point for sarcopenia in accordance with the study by Newman et al. [5]. This cutoff corresponded to a residual of −1.45 in the population studied herein.

Statistical analysis

Results were expressed as the mean (standard deviation) or percentages. Differences between the two groups (sarcopenia group and no sarcopenia) according to the two criteria were evaluated using the McNemar test, Student's *t* test, Mann–Whitney *U* test or the chi-square test.

Logistic regression models were used to analyse which factors were independently associated with sarcopenia regarding the two criteria. Only those variables significantly associated ($P < 0.05$) with sarcopenia in the univariate analysis were included in the logistic regression models. Lean mass was not included as an independent variable for both criteria and neither was the fat mass for ASM adjusted for fat criteria. Because collinearity exists between BMD sites, sites were sequentially added to the logistic regression, and the best model was then selected. These findings are presented as adjusted prevalence ratios with corresponding 95 % confidence intervals (95 % CI). Significance was set at $P < 0.05$. All analyses were performed using Stata 9.0 software.

Results

The mean age of the 611 women studied was 73.22 ± 5.21 years, 389 (63.7 %) White, 206 (33.7 %) Black or mulatto and 16 (2.6 %) Asian. The mean weight and height were, respectively, 64.75 ± 12.94 kg and 1.50 ± 0.06 m. The mean BMI was 28.67 ± 5.20 kg/m², with 213 subjects (34.9 %) classified as overweight (BMI ≥25 and <30 kg/m²) and 235 (38.5 %) as obese (BMI ≥30 kg/m²), according to the WHO classification [23]. Using the BMI classification adjusted for

ageing [24], 363 women (59.4 %) were classified as overweight or obese (BMI >27 kg/m²).

Prevalences of sarcopenia and overweight/obesity

The frequency of sarcopenia was significantly lower (3.7 %) using ASM/h² than ASM adjusted for fat (19.9 %) ($P<0.0001$). Twenty-two individuals were considered sarcopenic by both methods, 100 women were considered sarcopenic by ASM adjusted for fat criteria and not by ASM/h², while only one woman was classified as sarcopenic by the ASM/h² definition and not by ASM adjusted for fat criteria. The distribution of subjects according to the presence or absence of sarcopenia, using each method, is shown in Fig. 1.

The distribution of individuals according to the BMI categories is presented in Figs. 2 and 3. We must also note that, according to the WHO classification of BMI [23], less than 5 % (1/23) of those classified as sarcopenic by ASM/h² were overweight or obese (Fig. 2a), whereas 60 % (74/122) of those individuals considered sarcopenic based on the ASM adjusted for fat criteria had this complication (Fig. 2b). Using the cutoff points proposed by Lipschitz [24], a similar distribution was observed: less than 5 % (1/23) of women considered sarcopenic by ASM/h² (Fig. 3a) and more than 45 % (55/122) of sarcopenic women classified as sarcopenic by ASM adjusted for fat criteria (Fig. 3b) were classed as overweight or obese.

Risk factors according to ASM/h² criteria

Women with sarcopenia had lower weight, lower BMI and higher frequency of alcohol intake compared to women without sarcopenia (Table 1). In relation to the laboratory variables, only the eGFR was significantly lower in cases of

sarcopenia. No association between 25OHD categories and mean vitamin D levels and sarcopenia was observed (Table 1). Considering the blood samples collected among the seasons, similar distribution of sarcopenic subjects was observed among the seasons (spring and summer, 47.8 % compared with autumn and winter, 52.2 %, $P=0.63$).

All DXA bone parameters, except the L1 L4 T-score, were significantly lower in the sarcopenia group (Table 1). Regarding the DXA body composition, total lean mass, total fat mass and percentage of fat mass were lower in the individuals with sarcopenia.

The logistic regression model, after due adjustments for age, has shown that the femoral neck T-score (OR, 1.90; 95 % CI 1.06 3.41; $P=0.03$) and current alcohol intake (three or more units daily) (OR, 4.13; 95 % CI 1.18 14.45, $P=0.03$) remained significantly associated with sarcopenia.

Risk factors according to ASM adjusted for fat criteria

The sarcopenia group had a higher frequency of White race, lower weight and lower BMI compared to non-sarcopenic subjects. Concerning laboratory parameters, only creatinine was significantly lower in the sarcopenia group compared to subjects without this condition. No association between 25OHD categories and mean vitamin D levels and sarcopenia was observed (Table 2). Considering the blood samples collected among the seasons, similar distribution of sarcopenic subjects was observed among the seasons (spring and summer, 52.5 % vs. autumn and winter, 47.5 %, $P=0.95$).

Out of the DXA parameters, the total lean mass was lower in individuals with sarcopenia, while the percentage of fat mass was higher in this group (Table 2). The logistic regression model, after due adjustments for age, showed that White race (OR, 1.81; 95 % CI 1.15 2.84; $P=0.01$) and

Fig. 1 Distribution of individuals according to the two sarcopenia criteria

Fig. 2 **a** Classification of individuals according to BMI categories (WHO criteria), comparing sarcopenic and non-sarcopenic women in each criteria, using ASM/h². **b** Classification of individuals according to BMI categories (WHO criteria), comparing sarcopenic and non-sarcopenic women in each criteria, using ASM adjusted for fat

creatinine (OR, 0.21; 95 % CI 0.07–0.63; $P=0.005$) remained significantly associated to sarcopenia.

Comparison between sarcopenic women according to ASM/h² and ASM adjusted for fat criteria

Women with sarcopenia according to ASM/h² criteria presented lower weight, BMI, femoral neck T-score, total femur T-score, lean mass, fat mass and percentage of fat mass compared to sarcopenic women according to the criteria of ASM adjusted for fat (Table 3).

Discussion

Our study has shown that the criteria based on ASM adjusted for fat seems to be more appropriate for identifying

Fig. 3 **a** Classification of individuals according to BMI categories (Lipschitz's criteria), comparing sarcopenic and non-sarcopenic women in each criteria, using ASM/h². **b** Classification of individuals according to BMI categories (Lipschitz's criteria), comparing sarcopenic and non-sarcopenic women in each criteria, using ASM adjusted for fat

sarcopenia in community-dwelling older women with high prevalence of overweight and obesity and distinct associated factors. The great advantage of the design of the present study is the evaluation of a large population of individuals over 65 years old, as the highest prevalence of sarcopenia and frailty syndrome occurs after this age [5–8, 28]. In fact, the inclusion of younger patients may hamper the interpretation of risk factors [7, 8, 29], given that age-related factors for sarcopenia are expected to be distinct according to the age bracket. In addition, the use of the community rather than subjects in hospitals or institutions reduces other confounding variables relevant for sarcopenia [30, 31]. In this regard, an evaluation of general health has shown that

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Table 1 Clinical, laboratory and DXA parameters in women with and without sarcopenia according to ASM/h² criteria

	Sarcopenia (n=23)	No sarcopenia (n=588)	P
Age, years	74.34±4.42	73.20±5.23	0.11
Race (White), %	60.9	63.8	0.32
Height, m	1.49±0.06	1.50±0.06	0.49
Weight, kg	47.70±7.90	65.41±12.64	<0.001
BMI, kg/m ²	21.4±2.83	29.0±5.06	<0.001
Alcohol (≥3 U/day), %	17.4	5.3	0.03
Current smoking, %	17.4	9.9	0.27
Low physical activity, %	17.4	8.3	0.17
Falls (>1/year), %	26.1	38.1	0.24
Personal history of fracture, %	17.4	19.9	0.99
Radiographic vertebral fracture, %	26.1	30.1	0.68
Diabetes mellitus, %	13.0	23.3	0.25
Hypertension, %	56.5	73.0	0.08
Cardiovascular event, %	17.4	13.1	0.53
Calcium, mg/dl	9.47±0.47	9.43±0.45	0.76
Phosphorus, mg/dl	3.57±0.49	3.52±0.46	0.48
Alkaline phosphatase, U/L	199.17±137.64	187.82±54.90	0.33
iPTH, pg/dl	52.43±54.95	40.90±18.95	0.77
25OHD, ng/ml	19.27±11.09	18.44±8.97	0.76
25OHD ≥30 ng/ml, %	4.4	11.2	0.36
25OHD 21–29 ng/ml, %	34.7	24.0	
25OHD ≤20 ng/ml, %	60.9	64.7	
Creatinine, mg/dl	0.91±0.26	0.94±0.20	0.23
Creatinine clearance, ml/min	51.30±16.04	67.65±21.03	<0.001
Albumin, g/dl	4.41±0.29	4.38±0.27	0.62
Spine T-score	-2.67±1.49	-2.25±1.62	0.36
Femoral neck T-score	-2.60±0.72	-1.83±1.06	<0.001
Total femur T-score	-2.20±0.74	-1.35±1.04	<0.001
Lean mass, g	30,192.6±3,285.9	39,185.4±5,675.7	<0.001
Fat mass, g	15,858.9±5,414.0	24,430.5±7,780.2	<0.001
Fat mass, %	32.70±6.17	36.71±5.76	<0.001

Table 2 Clinical, laboratory and DXA parameters in women with and without sarcopenia according to ASM adjusted for fat criteria

	Sarcopenia (n=122)	No sarcopenia (n=489)	P
Age, years	73.68±4.97	73.11±5.26	0.15
Race (White), %	74.6	60.9	0.001
Height, m	1.51±0.06	1.50±0.06	0.11
Weight, kg	62.02±13.06	65.43±12.84	0.006
BMI, kg/m ²	27.11±5.13	29.06±5.15	<0.001
Alcohol (≥3 U/day), %	7.4	5.3	0.38
Current smoking, %	9.8	10.2	0.90
Low physical activity, %	11.5	8.0	0.41
Falls (>1/year), %	43.4	36.2	0.14
Personal history of fracture, %	23.8	18.8	0.22
Radiographic vertebral fracture, %	28.7	30.3	0.73
Diabetes mellitus, %	19.7	23.7	0.34
Hypertension, %	73	72.2	0.87
Cardiovascular event, %	11.5	13.7	0.52
Calcium, mg/dl	9.45±0.49	9.42±0.44	0.66
Phosphorus, mg/dl	3.55±0.47	3.52±0.46	0.62
Alkaline phosphatase, U/L	188.97±77.94	188.08±54.63	0.67
iPTH, pg/dl	41.61±27.30	41.26±19.75	0.71
25OHD, ng/ml	19.22±10.47	18.29±8.66	0.70
25OHD ≥30 ng/ml, %	13.9	10.3	0.40
25OHD 21–29 ng/ml, %	21.3	25.2	
25OHD ≤20 ng/ml, %	64.8	64.6	
Creatinine, mg/dl	0.89±0.21	0.95±0.20	0.001
Creatinine clearance, ml/min	67.76±22.75	66.86±20.67	0.81
Albumin, g/dl	4.41±0.27	4.37±0.28	0.09
L1-L4 T-score	-2.12±1.54	-2.30±1.64	0.21
Femoral neck T-score	-1.88±1.09	-1.86±1.05	0.60
Total femur T-score	-1.49±0.99	-1.35±1.05	0.18
Lean mass, g	35,471.7±5,341.9	39,688.9±5,680.7	<0.001
Fat mass, g	24,570±8,090	23,990±7,820	0.72
Fat mass %	38.97±5.38	35.97±5.78	<0.001

community-dwelling older Brazilian individuals took exercise more regularly than institutionalised ones [32]. Another important feature of our study is gender restriction given that risk factors for sarcopenia, osteoporosis and fractures are different in men and women, with dissimilar low skeletal muscle mass (ASM) cutoffs [2, 5, 8, 28, 30].

The prevalence of sarcopenia using ASM/h² criteria is lower when compared to other countries including Asian and Hispanic populations [6, 33–35]. The most likely explanation for this is methodological, as the ASM/h² definition cannot adequately identify overweight or obese people as sarcopenic. Indeed, most of the individuals in this study were overweight or obese. Only one subject in this category was identified as sarcopenic by ASM/h² contrasting with more than half of those overweight/obese women

who were diagnosed as sarcopenic based on the criteria of ASM adjusted for fat. In fact, another study also showed that older subjects with a BMI higher than 21 kg/m² have a lower risk of being sarcopenic using ASM/h² criteria [30].

The WHO recommends the same cutoffs of BMI for adults aged 18 and over [23]. On the other hand, Lipschitz proposed another classification considering the body composition changes resulting from ageing, since older people have decreased height, less body water and a higher percentage of fat when compared with adults. Thus, this recommendation modifies the cutoff point for the definition of underweight (18 to 22 kg/m²) and overweight (25 to 27 kg/m²) [24]. The higher prevalence of sarcopenic women with overweight/obesity using the criteria of ASM adjusted for fat, compared with

Table 3 Clinical, laboratory and DXA parameters in sarcopenic women comparing ASM/h² and ASM adjusted for fat criteria

	ASM/h ² (n=23)	ASM adjusted for fat (n=122)	P
Age, years	74.34±4.42	73.68±4.97	0.53
Race (White), %	60.9	74.6	0.20
Height, m	1.49±0.06	1.51±0.06	0.15
Weight, kg	47.70±7.90	62.02±13.06	0.006
BMI, kg/m ²	21.4±2.83	27.11±5.13	<0.001
Alcohol (≥3 U/day), %	17.4	7.40	0.13
Current smoking, %	17.4	9.80	0.28
Low physical activity, %	17.4	11.5	0.48
Falls (>1/year), %	26.1	43.40	0.16
Non-vertebral fracture, %	17.40	23.80	0.59
Radiographic vertebral fracture, %	26.1	28.7	0.99
Diabetes mellitus, %	13.04	19.7	0.56
Hypertension, %	56.52	73	0.13
Cardiovascular event, %	17.40	11.5	0.48
Calcium, mg/dl	9.47±0.47	9.45±0.49	0.88
Phosphorus, mg/dl	3.57±0.49	3.55±0.47	0.84
Alkaline phosphatase, U/L	199.17±137.64	188.97±77.94	0.60
iPTH, pg/dl	52.43±54.95	41.61±27.30	0.15
25OHD, ng/ml	19.27±11.09	19.22±10.47	0.97
Creatinine, mg/dl	0.91±0.26	0.89±0.21	0.76
Creatinine clearance, ml/min	51.30±16.04	67.76±22.75	0.001
Albumin, g/dl	4.41±0.29	4.41±0.27	0.93
Spine T-score	-2.67±1.49	-2.12±1.54	0.12
Femoral neck T-score	-2.60±0.72	-1.88±1.09	0.002
Total femur T-score	-2.20±0.74	-1.49±0.99	0.001
Lean mass, g	30,192.6±3,285.9	35,471.7±5,341.9	<0.001
Fat mass, g	15,858.9±5,414.0	24,570±8,090	<0.001
Fat mass %	32.70±6.17	38.97±5.38	<0.001

the criteria of ASM/h², was observed regardless of the cutoff used for the definition of overweight/obesity (25 or 27 kg/m²).

This issue is relevant since sarcopenic obesity has been associated with reduced walking speed and functional limitation [36, 37]. Moreover, some studies have demonstrated that obesity and muscle impairment act synergistically on the risk of functional incapacity, and sarcopenic obese subjects seem to be more disabled than people who are just obese or sarcopenic [38]. This may also be explained by the fact that, in obese people, lean body mass is always higher than in slim subjects because both lean mass and fat mass increase with weight gain. Normally, an increase in lean mass is expected to accompany an increase in fat mass by a ratio of approximately 1:4 [39]. Due to this dependence of lean mass on fat mass, the adequacy of an individual's lean mass cannot be gauged in isolation. Therefore, obese subjects may not seem sarcopenic, as their muscle mass is actually inadequate for the size of their body and physical performance. Although the functional status has not been evaluated in our population, nevertheless the recommended cutoff for ASM adjusted for fat criteria used herein is

probably related to disability as also has been reported in previous studies [5, 9].

In addition, sarcopenic obesity has been associated with increased cardiovascular risk [33, 35, 40] and mortality [41, 42]. The underlying mechanism is probably associated with the known proinflammatory state induced by visceral obesity [42], including muscle inflammation generated by fat infiltration, which may enhance the loss of muscle quality in older obese people [35, 43, 44].

We described an equation, based on the linear regression models, which allows the calculation of the expected ASM according to total fat mass. The result obtained from this formula should be subtracted from the ASM obtained by DXA, and this result is the residual of the ASM. Whether this residual is less than -1.45, we considered the woman is sarcopenic. Our sample was characterised by homogenous selection of the group; all subjects lacked vitamin supplementation, were from the same gender, and all were living independently. Our sample is, in fact, representative of the Brazilian older population according to the Brazilian Institute of Geography and Statistics (IBGE) [45], as reported in our previous studies with the same population (SPAH) [15, 46, 47]. Thus, this equation can be applied to Brazilian females aged over 65 years with a residual less than -1.45 for the sarcopenia cutoff point.

As for features related to sarcopenia, we found different factors according to each criterion. The probable explanation for this is the distinct group of subjects selected by each criterion. In this regard, the ASM/h² criteria included only slim people as sarcopenic, while using the ASM adjusted for fat, only a minority of sarcopenic women were underweight or of normal weight. It is therefore expected that the two groups have different risk factors for sarcopenia. The femoral neck T-score was associated with sarcopenia as determined by the ASM/h² method. This finding is most likely related with lower BMI, given that this parameter is a recognised risk for osteoporosis and fractures [48]. In contrast, a higher T-score is expected in sarcopenic subjects, according to the criteria of ASM adjusted for fat, in view of the fact that a higher fat mass will result in a greater BMD [49]. Furthermore, alcohol intake (three or more units daily) was also associated with sarcopenia, according to the ASM/h². This is a relevant finding, as the prevalence of alcohol consumption is high in the general population, including older age groups [50]. In addition, chronic alcohol consumption is associated with reduced lean body mass, and lower lean body mass is related to mortality among alcoholics [51]. We analysed the alcohol intake as a dichotomous variable, considering three or more units of alcohol daily as being a significant alcohol intake, the same cutoff point used for the risk of osteoporosis and fractures [19].

The association between sarcopenia and alcohol intake was observed only for the criteria based on ASM/h² and not

for the criteria of ASM adjusted for fat. This is due to the fact that chronic alcohol users tended to be thinner than individuals with no alcohol intake, and the criteria based on ASM/h^2 is able to identify only thin people as sarcopenic.

Regarding the criterion of ASM adjusted for fat, we have confirmed and extended the previous observation that the non-White ethnic group was found to be protective for sarcopenia [5]. We also demonstrated that serum creatinine was also a protective factor. Creatinine is the expression of muscle creatinine content and total muscle mass of the subject, and individuals with less muscle mass tend to have lower creatinine values [52, 53]. This result may be useful in clinical practice, as serum creatinine is a routine laboratory examination and, hence, low levels may be predictive of sarcopenia.

We concluded that, among overweight and obese women, the criterion of ASM adjusted for fat seems to be more appropriate for the diagnosis of sarcopenia. This has relevant public health implications, considering the risk factors identified herein and also the high prevalence of overweight and obesity among older women.

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Conflicts of interest None.

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ORIGINAL ARTICLE

Vertebral Fracture Assessment by Dual X-Ray Absorptiometry: A Valid Tool to Detect Vertebral Fractures in Community-Dwelling Older Adults in a Population-Based Survey

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Objective. Vertebral fractures are associated with higher morbidity and mortality. Since 70% of vertebral fractures are clinically silent, a radiologic image of the spine has to be acquired for the diagnosis. The aim of this study was to compare the performance of Vertebral Fracture Assessment (VFA) by dual x-ray absorptiometry (DXA) with radiographs to identify vertebral fractures in community-dwelling older adults.

Methods. A total of 429 older adults (ages ≥ 65 years) were enrolled in this cohort. VFA by DXA measurements were evaluated by 2 expert rheumatologists by consensus, and spine radiographs were analyzed according to the semiquantitative method by an expert radiologist. The correlation between VFA and spine radiographs to identify vertebral fractures was analyzed by kappa scores.

Results. The prevalence of vertebral fractures in VFA and radiographs was 29.1% and 29.4%, respectively ($P = 0.99$). The frequency of unavailable vertebrae was significantly lower in spinal radiographs than in VFA (0.9% and 5.6%, respectively; $P < 0.001$), particularly in T4–T6. According to VFA, 5,013 vertebrae (96%) were identified as normal and 144 (2.7%) had grade 1, 58 (1.1%) had grade 2, and 12 (0.2%) had grade 3 fractures. The sensitivity of VFA was 72.9% and the specificity was 99.1% to identify vertebral fractures. The sensitivity increased to 92% and the specificity increased to 99.9% when excluding grade 1 deformities. A good correlation between VFA and radiographs ($\kappa = 0.74$) was observed, and the exclusion of grade 1 resulted in even better agreement ($\kappa = 0.84$).

Conclusion. In community-dwelling older adults, VFA and radiographs had comparable performances in identifying vertebral fractures, particularly if mild deformities are excluded. Therefore, this methodology is a feasible and promising alternative to improve the management of patients with a high risk of osteoporotic fractures.

INTRODUCTION

Vertebral fractures have been reported in approximately one-third of the older population (1), a prevalence comparable to that observed in female (27.5%) and male (31.8%) community-dwelling older Brazilian subjects (2).

Vertebral fractures are associated with higher morbidity and mortality in the general population. Indeed, the presence of a vertebral fracture increases the risk for new

vertebral fractures from 3- to 12.6-fold and increases the risk for nonvertebral fractures from 1.6- to 4-fold (3–6). Moreover, the survival rate of patients with vertebral fractures is lower compared to those without fractures, with a risk of death increased by 2.5-fold in men and women (7–9).

Since 70% of vertebral fractures are clinically silent (6), radiologic images of the spine have to be acquired for the

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Significance & Innovations

- This article provides clinically important results because it shows that the Vertebral Fracture Assessment (VFA) by dual x-ray absorptiometry (DXA) is a valid method and has excellent reproducibility for the diagnosis of vertebral fractures. Being a tool that might be used concomitantly with the measurement of bone mineral density by DXA, it has an undoubted practical advantage. In addition, compared to spine radiographs, the patients are exposed to a lower load of radiation with VFA.
- This study is very important for clinical practice for all rheumatologists, who usually treat patients with a high probability of having vertebral fractures, although 70% of these fractures are asymptomatic.

diagnosis, and their detection is an indication for osteoporosis treatment (10). Spine radiographs remain the gold standard method, but lateral spine imaging obtained by dual x-ray absorptiometry (DXA) devices has emerged as an alternative assessment for the diagnosis of vertebral fractures (11–16). Most available studies demonstrating the effectiveness of Vertebral Fracture Assessment (VFA) by DXA, however, have included only women with a specific indication for spine radiographs (height loss, risk factors for osteoporosis and back pain, and long-term corticosteroid therapy) and postmenopausal women participating in osteoporosis treatment trials, precluding a definitive conclusion about the overall specificity and sensitivity of this method. Moreover, in general, the mean age in these studies has been <70 years and the studies have included smaller samples. There are few studies with male subjects and community-dwelling people (16–21).

Therefore, the aim of this study was to compare VFA by DXA and radiograph performances to identify vertebral fractures in healthy community-dwelling older men and women.

SUBJECTS AND METHODS

Subjects. This study is part of a previous epidemiologic project (2), including a population-based survey (São Paulo Ageing & Health [SPAH] study). This study was conducted from June 2005 to July 2009 and involved individuals ages ≥ 65 years living in the Butanta district, located in the western area of São Paulo. All individuals were apparently healthy and showed no evidence of malabsorption, chronic diarrhea, hepatic disease, severe chronic diseases, or cancer.

Four hundred twenty-nine subjects (259 women and 170 men) participating in the SPAH study were included in this study. For each individual, age, height, weight, and body mass index (BMI; calculated as kg/m^2) were obtained. A specific questionnaire, including the assessment of current thoracic/lumbar pain, was completed.

Assessment of vertebral fractures. All study participants who agreed to participate and who provided signed informed consent had bone densitometry of the hip and spine and a VFA scan of the thoracolumbar spine performed using the same DXA device (Discovery model, Hologic), with subjects in the supine position. All DXA measurements were performed by the same experienced technologist (LT). On that same day, standard lateral thoracic and lumbar spine radiographs were taken using a 40-inch tube-to-film distance centered at T7 and L2. These radiographs were not digitized.

All VFA and radiographic images were independently evaluated by 2 experienced rheumatologists (DSD, JBL) and 2 expert skeletal radiologists (MEK), respectively. For the identification of vertebral fractures, in both methods, the readers evaluated each T4–L4 vertebrae image to decide whether it contained a fracture. A consensus was reached between the readers for any difference of interpretation. Nonvisible vertebrae were excluded. Only adequately visualized vertebrae were analyzed for deformity using the Genant semiquantitative approach (22). Each identified fractured vertebra was classified by grade based on the Genant semiquantitative scale, where mild (grade 1) = a reduction of 20–25% of anterior, middle, and/or posterior height relative to the adjacent vertebral bodies; moderate (grade 2) = a reduction of 26–40% in any height; and severe (grade 3) = a reduction of >40% in any height.

Statistical analysis. The performance of VFA in the diagnostic evaluation of vertebral fractures was compared to that of radiographs (gold standard). All of the analyses were performed for the entire group, but men and women were also analyzed separately.

The number of unreadable vertebrae was compared between the 2 methods using McNemar's test. The vertebral visibility between different spine segments was compared by the chi-square test. Factors affecting vertebral visibility (i.e., sex, height, and BMI) were tested using Fisher's exact tests for the categorical variable and Spearman's correlations for continuous variables.

To verify the reliability between the readers for each method, a random subsample of 60 VFA and radiographic images was independently evaluated by the 2 rheumatologists and the 2 radiologists, respectively. A kappa score for the interrater reliability between the readers for VFA and radiographs was expressed using the kappa statistic. Agreements between the readers were high, with interobserver kappa coefficients of 0.78 for VFA scans and 0.82 for radiographs.

At the vertebral level, the overall agreement between VFA and radiographs for evaluable vertebrae, taking into account the presence or absence of vertebral fracture and the grade of fracture, was expressed using the kappa score. The sensitivity and specificity of VFA with exact 95% confidence intervals (95% CIs), diagnostic accuracy of VFA, positive and negative likelihood ratios (LRs), and positive and negative predictive values were calculated. All of these analyses were also performed excluding mild (grade 1) fractures to verify if this would result in an improvement of performance.

At the patient level, subjects were classified as fractured (at least 1 fracture in visible vertebrae) or nonfractured (all visible vertebrae from T4–L4 with no fracture). The overall agreement between the methods (considering individuals with fractured and nonfractured vertebrae) was expressed using the kappa score. Again, the sensitivity and specificity with exact 95% CIs, diagnostic accuracy of VFA, positive and negative LRs, and positive and negative predictive values were calculated. All analyses were also performed excluding mild (grade 1) fractures to verify if this would result in an improvement of performance.

Moreover, a random subsample of 100 spine radiographic images was evaluated regarding the adjacent disc spaces for osteophyte formation and overall osteoarthritis severity, according to a modification of the Kellgren/Lawrence scale, as normal, mild, or moderate/severe (23). To describe the influence of disc space osteoarthritis on fracture assessment at the vertebral level, an agreement by kappa score between VFA and radiographs for detecting fractures before and after eliminating vertebrae with moderate or severe osteoarthritis in both the superior and inferior disc spaces was performed. The sensitivity and specificity of VFA compared to radiographs were also calculated. Significance was set at *P* values less than 0.05. All analyses were performed using Stata software, version 9.0.

RESULTS

Subject characteristics. Two hundred fifty-nine women with a mean $\pm$ SD age of 73.5 ± 5.4 years and 170 men with a mean $\pm$ SD age of 72.3 ± 4.5 years were studied. The mean $\pm$ SD height and weight for women were 150 ± 6.3 cm and 64.5 ± 14.1 kg, respectively, and for men were 163.1 ± 7.4 cm and 70.4 ± 12.5 kg, respectively. The mean $\pm$ SD BMI was 28.5 ± 5.6 kg/m² for women and 26.4 ± 3.8 kg/m² for men.

Figure 1. Proportion of vertebrae satisfactorily visible on Vertebral Fracture Assessment scans (T4–T6 versus T7–L4; *P* < 0.001 by chi-square test).

Table 1. VFA versus radiographic fracture interpretation (at the vertebral level)*

VFA	Radiographs				Total
	Normal	Grade 1	Grade 2	Grade 3	
Normal	4,952	44	15	2	5,013
Grade 1	42	86	16	0	144
Grade 2	5	4	43	6	58
Grade 3	0	0	0	12	12
Total	4,999	134	74	20	5,227

* VFA = Vertebral Fracture Assessment.

Visibility of the spine. Of 5,577 potentially readable vertebrae from T4–L4, the frequency of unavailable vertebrae was significantly lower in spine radiographs than in VFA (0.9% and 5.6%, respectively; *P* < 0.001). On radiographic films, 92.3% of the unreadable vertebrae (48 of 52) were located in the segment T4–T6 and 99.9% of the vertebral bodies (4,286 of 4,290) from T7–L4 were effectively visualized (*P* < 0.001). On VFA scans, nonvisible vertebrae were also mostly located in T4–T6 (170 [54.8%] of 310) and, in the segment T7–L4, 96.7% of the vertebral bodies (4,150 of 4,290) had good visibility to assess the presence of fractures (*P* < 0.001). The visibility of the spine by VFA is shown in Figure 1. There was a significant difference in the frequency of visible vertebrae between segments T4–T6 and T7–L4 (*P* < 0.001). Sex (*P* = 0.33), height (*P* = 0.05), and BMI (*P* = 0.84) did not affect the visibility of the vertebrae by VFA (data not shown).

Identification of vertebral fractures. At the vertebral level. On spine radiographs, 4,999 vertebrae (95.6%) were normal and 134 (2.5%) had grade 1, 74 (1.3%) had grade 2, and 20 (0.4%) had grade 3 fractures. According to VFA, 5,013 vertebrae (96%) were identified as normal and 144 (2.7%) had grade 1, 58 (1.1%) had grade 2, and 12 (0.2%) had grade 3 fractures. Comparison between VFA and radiographs is shown in Table 1. Concerning the concordance between VFA and vertebral fractures, 4,952 vertebrae (94.8%) were normal and 86 (1.6%) had grade 1, 43 (0.8%) had grade 2, and 12 (0.2%) had grade 3 fractures on both methods.

There was good overall agreement between VFA and radiographs at the vertebral level ($\kappa = 0.74$) and by grade of vertebral fracture ($\kappa = 0.68$). Both results were even better when grade 1 deformities were excluded ($\kappa = 0.84$ and $\kappa = 0.80$, respectively). Further analysis by vertebral levels revealed good to very good agreement for all levels ($\kappa = 0.61$ – 0.83). Analysis of solely grades 2 and 3 fractures also resulted in a better agreement, except for the T4–T6 levels (Table 2).

The overall sensitivity of VFA for fracture diagnosis was 72.9% (95% CI 66.7–78.6%) and the specificity was 99.1% (95% CI 98.8–99.3%). Therefore, the diagnostic accuracy of VFA compared to radiographs was 97.9% (95% CI 97.8–98%). The positive and negative predictive values for fractures using VFA were 78.0% (95% CI 71.9–83.4%) and 98.8% (95% CI 98.4–99.1%), respectively. Furthermore, when only grades 2 and 3 fractures were considered, the

Table 2. Agreement between Vertebral Fracture Assessment and radiographs*

Vertebral level	All grades of fractures	Including only grades 2 and 3 fractures
T4	NA	NA
T5	0.66	0.49
T6	0.61	-0.01
T7	0.67	1
T8	0.73	0.83
T9	0.72	0.89
T10	0.66	NA
T11	0.74	0.74
T12	0.78	1
L1	0.76	0.91
L2	0.83	0.84
L3	0.68	0.71
L4	0.79	0.80

* Values are the kappa statistic. NA = not applicable (no vertebral fracture was detected on the T4 and T10 levels).

sensitivity of VFA increased to 92.0% (95% CI 86.0–99.0%), whereas the other performance parameters remained equivalent to the analysis, including grade 1 deformities, with specificity of 99.9% (95% CI 99.8–100%), diagnostic accuracy of 99.5% (95% CI 99.4–99.6%), positive predictive value of 77.0% (95% CI 68.0–86.0%), and negative predictive value of 99.6% (95% CI 99.4–99.8%). The positive and negative LR of VFA were 77.5 (95% CI 57.7–104) and 0.27 (95% CI 0.22–0.34), respectively. The concordance between the methods was higher in the case of grade 2 or 3 fractures, with a positive LR of 255.4 (95% CI 160.1–406.7) and a negative LR of 0.08 (95% CI 0.03–0.18). The positive LR was less for grade 1 fractures, where 42 nonfractured vertebrae on radiographs were considered as having grade 1 fractures on VFA and 44 grade 1 fractures on radiographs were considered as normal using VFA (Table 1).

Analyzing by vertebral levels, the sensitivity and positive predictive value decreased from the lumbar spine to the upper thoracic spine. In contrast, the specificity and negative predictive value remained above 95%. Of note, exclusion of grade 1 fractures improved the diagnostic value of VFA to detect fractures in each vertebral level (Table 3).

Analyzing female and male subjects separately, the kappa scores between VFA and radiographs, with all grades of fractures and excluding grade 1 deformities, were 0.75 and 0.86 for female subjects and 0.73 and 0.82 for male subjects, respectively. The diagnostic performance of VFA compared to radiographs also showed similar results to those found for the entire population (Table 4).

Concerning osteoarthritis analysis, there was a slight improvement in the kappa score between VFA and radiographs with all grades of fractures before and after eliminating the vertebrae with osteoarthritis (0.77 and 0.83, respectively). Moreover, no improvement in the sensitivity (83%; 95% CI 66–99% and 84%; 95% CI 68–99%, respectively) and specificity (82%; 95% CI 69–94% and 82%;

95% CI 70–94%, respectively) was observed before and after eliminating the vertebrae with osteoarthritis.

At the individual level. On VFA scan and spine radiographs, the prevalence of vertebral fractures was 29.1% (125 of 429 subjects) and 29.4% (126 of 429 subjects), respectively ($P = 0.99$). On VFA, the frequencies of vertebral fractures in women and men were 29.7% (77 of 259) and 28.2% (48 of 170), respectively ($P = 0.74$). On spine radiographs, 28.6% of women (74 of 259) and 30.6% of men (52 of 170) had vertebral fractures ($P = 0.65$). Separating by sex, there was no difference between VFA and radiographs related to the prevalence of vertebral fractures ($P = 0.69$ for women and $P = 0.5$ for men).

Using radiographs, among 126 individuals with fractures, 61 subjects (48.4%) presented only grade 1 deformities, 49 (38.9%) had at least one grade 2 fracture, and 16 (12.7%) had at least one grade 3 fracture. There was a mean $\pm$ SD of 1.9 ± 1.1 fractured vertebrae among subjects with fractures. On VFA scan, among 125 individuals with fractures, 76 subjects (60.8%) presented only grade 1 fractures, 39 (31.2%) had at least one grade 2 fracture, and 10 (8%) had at least one grade 3 fracture. There was a mean $\pm$ SD of 1.7 ± 1.1 fractured vertebrae among subjects with fractures. The overall agreement between VFA and radiographs was good ($\kappa = 0.75$), and it was higher after excluding grade 1 fractures ($\kappa = 0.91$).

The sensitivity of VFA was 81.7% (95% CI 73.9–88.1%) and the specificity was 92.7% (95% CI 89.2–95.4%). Therefore, the diagnostic accuracy of VFA compared to radiographs was 90.0% (95% CI 89.1–90.8%). The positive and negative predictive values for fractures using VFA were 82.4% (95% CI 74.6–88.6%) and 92.4% (95% CI 88.9–95.1%), respectively. The positive and negative LR of diagnosis of vertebral fracture by VFA were 11.3 (95% CI 7.5–17.0) and 0.20 (95% CI 0.14–0.28), respectively. Furthermore, the diagnostic performance of VFA was also better when only grades 2 and 3 fractures were considered, with sensitivity of 88.2% (95% CI 76.1–

Table 3. Diagnostic performance of Vertebral Fracture Assessment to detect grades 2 and 3 fractures by vertebral level*

Vertebral level	Sensitivity	Specificity	PPV	NPV
T4	NA	NA	NA	NA
T5	66.7	99.7	66.7	99.7
T6	50.0	99.7	80.0	98.9
T7	60.7	98.9	81.0	97.0
T8	72.0	98.7	78.3	98.1
T9	75.0	98.5	71.4	98.7
T10	62.5	99.5	71.4	99.3
T11	75.0	98.2	77.4	97.9
T12	85.7	98.0	75.0	99.0
L1	73.5	98.7	83.3	97.7
L2	80.0	99.5	88.9	99.0
L3	69.2	99.0	69.2	99.0
L4	80.0	99.5	80.0	99.5

* Values are the percentage. PPV = positive predictive value; NPV = negative predictive value; NA = not applicable (no vertebral fracture was detected on the T4 level).

Table 4. Diagnostic value of VFA to detect vertebral fractures by sex (at the vertebral level and the individual level)*

	Women				Men			
	All grades of fractures, vertebral level	All grades of fractures, individual level	Grade 1 fractures excluded, vertebral level	Grade 1 fractures excluded, individual level	All grades of fractures, vertebral level	All grades of fractures, individual level	Grade 1 fractures excluded, vertebral level	Grade 1 fractures excluded, individual level
Sensitivity, %	76.6	85.1	78.3	90.6	68.3	76.9	75.8	84.2
Specificity, %	99.0	92.4	99.9	99.9	99.2	93.2	99.8	99.1
Accuracy, %	98.1	90.3	99.6	98.5	97.7	88.2	99.5	96.9
PPV, %	76.0	81.8	94.7	99.9	81.2	83.3	89.3	94.1
NPV, %	99.0	94.0	99.7	98.3	98.4	90.2	99.6	97.3
Positive LR	74.5	11.3	1,170	NA	84.5	11.3	497	93.5
Negative LR	0.24	0.16	0.22	0.09	0.32	0.25	0.24	0.16

* VFA = Vertebral Fracture Assessment; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; NA = not applicable (no disagreement between VFA and radiographs concerning absence of grades 2 and 3 vertebral fractures in female subjects).

95.6%), specificity of 99.6% (95% CI 98–99.9%), diagnostic accuracy of 97.9% (95% CI 97.7–98.1%), positive predictive value of 97.8% (95% CI 88.5–99.9%), negative predictive value of 97.9% (95% CI 95.5–99.2%), positive LR of 248 (95% CI 35–1,759), and negative LR of 0.10 (95% CI 0.05–0.2).

Separating by sex, the kappa scores between VFA and radiographs with all grades of fractures and excluding grade 1 deformities were 0.77 and 0.94 for female subjects and 0.72 and 0.87 for male subjects, respectively. The diagnostic value of VFA to identify individuals with at least one vertebral fracture was similar, considering the entire population and separating by sex (Table 4).

None of the evaluated subjects had previous knowledge of having vertebral fractures. Moreover, concerning the history of back pain, 53% of older individuals reported this symptom. Only 17% of these subjects with back pain had radiographic vertebral fractures compared to 12% of individuals without back pain who had radiographic vertebral fractures ($P = 0.13$).

DISCUSSION

Our study showed a very good performance of VFA to detect prevalent vertebral fractures, with a high positive predictive value for fracture diagnosis and a high negative predictive value for fracture exclusion.

The biggest advantage of the present study design is the evaluation of a large population of solely individuals ages ≥ 65 years, since the highest risk of vertebral fractures occurs after this age (3–6). Furthermore, only community-dwelling subjects were included. Another advantage of this study is the individualized analysis by sex. VFA has previously received limited evaluation in men. Our results confirmed the excellent diagnostic value of VFA in men and women. Vallarta-Ast et al also demonstrated the utility of VFA, but in a population with specific indications for DXA (24).

The VFA evaluation strictly follows the International Society for Clinical Densitometry (ISCD) (25) recommendation that the diagnosis of vertebral fractures should be done by visual evaluation according to the semiquantitative

method (22), which has excellent inter- and intra-observer agreement. Although the semiquantitative approach depends mostly on the examiner's experience and training, it has the great advantage of being easily applicable in clinical practice, contrasting with morphometry, which is not reliable for diagnosis. The semiquantitative method demonstrated high accuracy for identifying grades 2 and 3 fractures, but demonstrated lower accuracy for identifying grade 1 deformities. Previous studies have suggested that grade 1 deformities do not, in fact, represent clinically significant fractures and do not confer increased risk of new fractures or higher mortality in these individuals (2,26,27). These changes would be related more to the aging process, including kyphosis and degenerative changes in the spine (28,29).

VFA by DXA has other clear benefits compared to conventional radiography. Besides the possibility of a simultaneous evaluation with lumbar and hip bone mineral density acquisition, it has the advantage of reducing the impact of parallax effects on fracture visualization. In addition, VFA delivers a much lower dose of radiation to the patient (entrance dose 30–50 μ Sv) than thoracic/lumbar spine radiographs (1,800–2,000 μ Sv) (30,31). VFA also has a lower cost than radiographs (\$44 versus \$92 in the US) (32). Good cost-effectiveness was demonstrated for this method (33,34).

We have confirmed previous studies (12,19,28,35,36) indicating that vertebral visibility in the upper thoracic spine (above T7) is the main limitation of VFA due to the restricted image resolution of the DXA device in this region. This was also true for radiographic assessment, although to a lesser extent. This limitation does not seem to be a significant disadvantage, since most vertebral fractures were located at the mid-lower thoracic and lumbar spine (37), where there is good visibility reinforcing the notion that VFA by DXA remains an important tool for clinical practice based on the high positive predictive value.

Importantly, the specificity and the negative predictive value were high (above 90%) at all vertebral levels. These findings have relevant clinical implications and emphasize that false-positive results are rare on VFA assessment.

and suggest that it is not necessary to perform spine radiographs if there is no vertebral fracture on VFA. On the other hand, we showed that the agreement (kappa statistic) between VFA and radiographs was much more inferior in the segments T4–T6, with a lower sensitivity and positive predictive value of VFA in this segment. This means that more false-negative results can occur at the upper thoracic spine.

The positive and negative LR were better for grades 2 and 3 fractures than grade 1 deformities, which is consistent with previous reports (19–21). These results indicate greater disagreement between the methods for the presence of mild fractures. We also extended a prior observation that sex, height, and BMI did not seem to influence spinal visibility (18,21).

The presence of an osteoporotic vertebral fracture on an image, even a subclinical image, is a formal indication for osteoporosis therapy, independently of bone mineral density (10). Therefore, knowledge of prevalent vertebral fractures can alter patient management decisions and result in initiation of therapy to reduce fracture risk in some patients who would not otherwise be treated. Cost-benefit analysis demonstrates that identifying and treating patients with vertebral fractures, even those with a densitometric classification of osteopenia, is cost effective (33,34). Therefore, the inclusion of VFA, concomitant with routine bone density testing, seems to prompt incorporation of knowledge into fracture risk estimation, which ultimately would optimize the management of patients with osteoporosis.

Nevertheless, vertebral deformities do not always correspond to vertebral fractures, and conventional radiography is the best way to identify and confirm these abnormalities in clinical practice. There are other potential differential diagnoses for vertebral deformities, such as osteoarthritis, diffuse idiopathic skeletal hyperostosis, Scheuermann's disease, congenital malformation, Paget's disease, and neoplastic and inflammatory changes. All of these causes can influence the morphology of the vertebrae and can therefore mimic fractures, leading to false-positive diagnoses of fractures (38). According to the 2007 ISCD official positions (25), VFA is designed to detect vertebral fractures and not other deformities. The presence of sclerotic or lytic changes or findings suggestive of conditions other than osteoporosis is an indication for following VFA with another imaging modality.

In this study, we did not see any clear improvement in the sensitivity and specificity of VFA relative to radiographs by excluding those vertebrae with moderate or severe osteoarthritis in the adjacent disc spaces, but this analysis was done in a smaller subsample. Also, our study has other limitations: first, we did not evaluate the influence of scoliosis in vertebral visibility, and second, considering that our study has a transversal design, we cannot establish the prevalence of clinical vertebral fractures (acute back pain). However, it is known that most vertebral fractures are diagnosed by radiologic images. Gehlbach et al, evaluating chest radiographs of older women who had been hospitalized for several causes, found that a few vertebral fractures had been identified by clinicians previously (39). Indeed, in our study, one-third of older subjects

had this condition, although no one had prior knowledge of having vertebral fractures.

In conclusion, in community-dwelling older adults, VFA had a performance comparable to radiographs to identify clinically relevant grades 2 and 3 vertebral fractures. This methodology is easily applicable and seems to be a promising alternative to spine radiographs, improving the management of patients with a high risk of osteoporotic fractures.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Pereira had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Domiciano, Pereira.

Acquisition of data. Domiciano, Figueiredo, Lopes, Kuroishi, Takayama, Caparbo, Fuller, Menezes, Scazufca.

Analysis and interpretation of data. Domiciano, Bonfa, Pereira.

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ORIGINAL ARTICLE

Prevalence of sarcopenia and associated risk factors by two diagnostic criteria in community-dwelling older men: the São Paulo Ageing & Health Study (SPAH)

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Abstract

Summary Sarcopenia is an aging syndrome that can be characterized by many criteria adjusted or not by fat mass. This study suggested that the optimal criteria should be selected according to body mass index (BMI) in older men and identified age, BMI, race, smoking, physical activity, hip bone mineral density (BMD) as risk factors for this syndrome.

Introduction This study aims to analyze the prevalence of sarcopenia and associated risk factors using appendicular skeletal mass (ASM)/height² and ASM adjusted for total fat mass criteria in older men from community.

Methods Three hundred ninety-nine men were included and answered a questionnaire about lifestyle and medical history. Individuals were classified by their BMI using the classification adjusted by age. Body composition and bone mineral density were measured by dual X-ray absorptiometry. Sarcopenia was classified according to both criteria. Logistic regression models were used to analyze risk factors associated with sarcopenia.

Results The mean BMI was 26.46 kg/m²; 12.5 % underweight, 43.6 % normal, and 43.9 % overweight/obese. Fifty-four (13.5 %) were considered sarcopenic by ASM/height² and 79 (19.8 %) by ASM adjusted for fat ($p=0.001$). Fifty-one (12.8 %) individuals had discordant sarcopenia classification: 13 were classified only by ASM/height² and 38 only by ASM adjusted for fat. Of the 13 subjects classified as sarcopenic only by ASM/height², 84.6 % (11/13) were underweight and solely one (7.7 %) was considered overweight/obese.

In contrast, of those 38 older men classified as sarcopenic only by ASM adjusted for fat, none were underweight and 53 % (20/38) were overweight/obese. Subjects classified as sarcopenic according to both criteria had the same risk factors in the final model analyses (age, BMI, race, smoking, physical activity, hip BMD; $p<0.05$).

Conclusion This study suggested that the optimal criteria for sarcopenia should be selected according to BMI in community-dwelling older men.

Keywords BMI · Body composition · Older men · Risk factors · Sarcopenia

Introduction

Sarcopenia is a severe syndrome associated with human ageing, and it is characterized by progressive loss of skeletal muscle mass, which results in decreased muscle strength and impairment of physical and functional capacity [1], in addition to being associated to increasing of cardiovascular risk and mortality [2–4]. Recently, the European Working Group on Sarcopenia in Older People considered sarcopenia as a geriatric syndrome [1].

The measure of appendicular mass consists on the main diagnosis tool evaluated by dual X-ray absorptiometry (DXA), which is the best method recommended in clinical practice [5]. The definition of sarcopenia proposed by Baumgartner in the population of New Mexico is the most widely used criteria in the literature. The ratio between appendicular skeletal muscle mass (ASM) (in kilograms) and height squared (height²) (in square meters), ASM/height², known as relative skeletal muscle mass index lower than 2 standard deviations or more below the normal means for a younger reference group measured using DXA defines sarcopenia [6]. In the New Mexico Aging Process Study, the cutoffs for defining sarcopenia (ASM/height²) were 7.26 kg/m² for men and 5.45 kg/m² for women. However, the

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prevalence of sarcopenia using $ASM/height^2$ was lower than expected, ranging from 3 to 16 %, probably due to the increasing prevalence of overweightness and obesity in many regions of the world [7–10].

Newman et al. proposed another method for defining sarcopenia, adjusting ASM for height and total fat mass and they found a higher prevalence of sarcopenia in the population, particularly among obese subjects (15.4 % men and 21.7 % women) compared with the frequencies found with the $ASM/height^2$ criteria [11]. These results suggested that ASM adjusted for fat criteria is potentially more appropriate to diagnose sarcopenia in overweight/obese individuals. In fact, our previous study demonstrated that in overweight/obese older women, ASM adjusted for fat criteria seems to be more accurate for sarcopenia diagnosis [12]. Interestingly, distinct risk factors for this syndrome were reported using both methods to evaluate our population of community-dwelling older adults, with high frequency of overweightness and obesity [13], according to body mass index [14]. There is, however, a lack of data regarding the comparison of these two methods in older men.

Therefore, the present study assessed the prevalence and risk factors associated with sarcopenia, using both criteria, $ASM/height^2$ and ASM adjusted for fat, in older men from a community.

Materials and methods

Subjects

This study was based on data from the São Paulo Ageing & Health Study (SPAH). Full details regarding the study population, assessments, and procedures have been previously reported [15]. Briefly, 2,266 older individuals were eligible and 2,072 (91.4 %) agreed to participate in the first phase of the study (2002–2003). In a second phase (2005 July to 2007 August), the participants were recruited again and 1,368 agreed to undergo new assessments regarding body composition and bone metabolism study. In the present investigation, only well-functioning older participants were analyzed; thus, 611 women and 399 men were interviewed and examined in sarcopenia SPAH study. Well-functioning older subjects, an inclusion criterion, was defined as individuals able to perform basic activities of daily living, to come to our center without walking difficulties, and with no life-threatening illness.

This study was approved by the local ethics committee (#426/06, #872/03), and all the participants read and signed an informed consent.

Clinical and vertebral fracture evaluation

Each subject was interviewed by a doctor and answered a detailed questionnaire to obtain information of lifestyle, medical

history, and data on putative risk factors of osteoporosis/fractures such as family history of fragility fracture, previous fragility fracture, history of falls during the last year, physical activity, alcohol use, current tobacco use, glucocorticoid use, presence of back pain, and dietary calcium.

Previous non-vertebral fragility fractures was determined in individuals who had experienced a fall from standing height or less after 50 years of age, and occurring at sites characteristic of bone fragility (for example, rib, forearm, humerus, and femur). Fractures occurring of the face, skull, ankle, elbow, and finger were not considered in this analysis [16]. Vertebral fractures were diagnosed from standard lateral thoracic and lumbar spine radiographs taken from all subjects and the images were evaluated by an expert skeletal radiologist and the fractures were classified according to Genant semiquantitative method [17].

Individuals were questioned about their history of falls during the last year; those who had two or more falls in the last 12 months were defined as chronic fallers [18]. An individual was deemed to be an alcohol user when current intake exceeded three units of alcohol per day [19].

Glucocorticoid use was defined as prednisone treatment of more than 5 mg/day for three or more consecutive months. A quantitative questionnaire resembling the National Health Interview Survey was also used to evaluate the physical activity of the subjects, and the results were expressed as a score ranging from 1 to 3. A score of 3 was assigned to subjects who exercised regularly (high physical activity); 2 was assigned to subjects who did not exercise regularly but participated in daily activities, such as housework, gardening, climbing or descending stairs, or walking to work or to the bus stop (moderate physical activity); and 1 was assigned to subjects who did not participate in any of the aforementioned activities on a daily basis (low physical activity) [20]. Total calcium intake was obtained when individuals were asked to quantify their consumption of milk or yogurt (in milliliters per day) and cheese (in grams per day) during the 7 days prior to the interview [21]. Race was defined based on self-reported race of second-generation ancestors, an approach previously used in the Brazilian population [22]. The height (without shoes) of each subject was measured to the nearest 0.1 cm with a wall-mounted stadiometer. The weight of each participant (without shoes, wearing only light clothing) was measured to the nearest 0.25 kg using a double-beam balance scale.

Body mass index (BMI) was calculated by dividing the subjects' weight (in kilograms) by their height squared (square meters). Individuals were classified by their BMI using the classification recommended by Lipschitz, adjusted by age [23]. This classification considers the body composition changes from ageing, namely underweight ($BMI < 22 \text{ kg/m}^2$), normal weight ($BMI \geq 22$ and $< 27 \text{ kg/m}^2$), and overweight/obese ($BMI \geq 27 \text{ kg/m}^2$).

Laboratory evaluation

Blood samples were collected under fasting conditions (between 8 and 10 a.m.) and stored at -70°C for later analysis.

The serum concentrations of calcium, phosphorus, alkaline phosphatase, creatinine, glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were determined using standard automated laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault equation [24]. The serum concentration of vitamin D (25OHD) was measured using a radioimmunoassay technique (DiaSorin, Stillwater, MN, USA) with a lower detection limit of 5 ng/mL. Vitamin D was expressed by the mean (standard deviation) and also by vitamin D categories according to the definitions of 2011 Endocrine Society Clinical Practice Guideline [25]. Intact parathyroid hormone serum concentrations were measured by immunoradiometric assay (ELSA-PTH, CIS bio international, France), with reference variations of 11–65 pg/mL.

Body composition and bone mineral density

Body composition and bone mineral density (BMD) were measured by dual X-ray absorptiometry (DXA) using Hologic densitometry equipment (Hologic Inc. Bedford, MA, USA, Discovery model), on the same day that laboratory sample and abdominal X-ray were obtained. BMD was measured at the following sites: lumbar spine, femoral neck, and total femur. All BMD measurements were performed by the same experienced technologist.

Appendicular skeletal mass was defined as the sum of arms and legs lean soft tissue masses, assuming that all non-fat and non-bone tissue is skeletal muscle. The total body fat was expressed in grams and as percentage of body weight.

The precision error for BMD measurements was determined based on standard International Society for Clinical Densitometry protocols [26].

Definitions of sarcopenia

For the purpose of this analysis, two measures of ASM were used to define sarcopenia: ASM relative to height squared and ASM relative to height and total fat mass.

Relative lean mass (LM) was first calculated using the criteria ($\text{ASM}/\text{height}^2$) proposed by Baumgartner [6, 27], and the cutpoint was $7.26 \text{ kg}/\text{height}^2$ (value for male). A second measure of relative LM was derived by adjusting for fat mass in addition to height [11]. Linear regression was used to model the relationship between ASM on height (in meters) and fat mass (in kilograms). The residuals of the regression were used to identify those with LM lower than the predicted value (given by an equation derived from the model), for an individual fat mass. A positive residual would indicate a relatively muscular individual,

whereas negative values would indicate relatively sarcopenic individuals. Our equation resultant from the model was as follows: $\text{ASM (kg)} = -20.67 + 22.48 \times \text{height (m)} + 0.177 \times \text{fat mass (kg)}$

The 20th percentile of the distribution of residuals was used as the cutpoint for sarcopenia according to ASM adjusted for fat. This cutoff corresponded to a residual of -2.06 in the population studied herein.

Statistical analysis

Results were expressed in mean (standard deviation) or percentages. The categorical variables were tested for their differences using Fisher's exact test, Chi-square, and test likelihood ratio. Student's *t* test or Mann–Whitney test were used to analyze the differences in the distribution of continuous variables. A kappa score between the two criteria was also done.

Logistic regression models were used to analyze which factors were independently associated with sarcopenia according to both criteria ($\text{ASM}/\text{height}^2$ and ASM adjusted for fat). Only variables significantly ($p \leq 0.05$) associated with sarcopenia in the univariate analysis were included in the final model. Because collinearity existed between BMD sites, they were sequentially added to the regression analysis and the best model was selected. These findings are presented as adjusted prevalence ratios with corresponding 95 % confidence intervals (95 % CI). The accuracy of $\text{ASM}/\text{height}^2$ criteria was 93 %, and the ASM adjusted for fat criteria was 83 %.

All analyses were performed using the SPSS (version 15.0) software.

Results

The mean age of the 399 men was 72.71 (5.06) years, the mean weight 70.27 (12.20) kg, and the mean height 162.58 (7.43) cm. The mean BMI was $26.46 (4.05) \text{ kg}/\text{m}^2$ and according to the BMI classification adjusted by aging, 12.5 % (50) were categorized as underweight ($\text{BMI} < 22 \text{ kg}/\text{m}^2$), 43.6 % (174) as normal ($\text{BMI} \geq 22$ and $\leq 27 \text{ kg}/\text{m}^2$), and 43.9 % (175) as overweight/obese ($\text{BMI} > 27 \text{ kg}/\text{m}^2$). The demographic, anthropometric, and clinical characteristics of the older men with and without sarcopenia by $\text{ASM}/\text{height}^2$ method are shown in Table 1 and these data by ASM adjusted for fat criteria are illustrated in Table 2.

Prevalence of sarcopenia according to $\text{ASM}/\text{height}^2$ and ASM adjusted for fat mass criteria

Of the 399 older men selected, 54 (13.5 %) were defined as sarcopenic by $\text{ASM}/\text{height}^2$ and 79 (19.8 %) by ASM adjusted for fat ($p=0.001$). The kappa coefficient between both criteria was 0.54 (95 % CI 0.43–0.65). Forty-one subjects were

Table 1 Demographic, clinical, and laboratorial data in older men with and without sarcopenia classified by the ratio of appendicular skeletal mass (ASM)/height²

Variables	Sarcopenia		<i>p</i> value ^a
	Yes <i>N</i> =54	No <i>N</i> =345	
Age, years	74.2 (6.6)	72.4 (4.7)	0.124
Black race, %	22.2	31.0	0.204
Height, cm	161.2 (9.2)	162.7 (7.1)	0.530
Weight, kg	55.6 (8.0)	72.3 (11.6)	<0.001
BMI, kg/m ²	21.3 (2.5)	27.2 (3.6)	<0.001
Alcohol, %	11.1	8.4	0.449
Alcohol, U/day	8.3 (13.1)	7.0 (15.0)	0.338
Current smoking, %	37	11.3	<0.001
Low physical activity, %	27	10	<0.001
History of falls, %	29.6	27	0.682
Number of falls/year	0.77 (2.0)	0.43 (0.97)	0.567
Fragility fractures, %	18.5	6.4	0.005
Diabetes mellitus, %	14.8	17.1	0.676
Arterial hypertension, %	51.9	56.5	0.520
Cardiovascular event, %	13	16.8	0.476
Calcium intake, mg	397.7 (319.3)	402.0 (316.5)	0.696
Alkaline phosphatase, U/L	202.8 (97.2)	171.4 (61.3)	0.017
25 OHD, ng/mL	20.6 (10.8)	21.3 (9.4)	0.549
eGFR, mL/min	45.7 (10.8)	61.0 (18.3)	<0.001
LDL-C, mg/dL	115.1 (36.3)	116.7 (34.2)	0.783
HDL-C, mg/dL	55.7 (12.0)	51.9 (13.2)	0.014
Triglycerides, mg/dL	106.5 (55.5)	139.5 (122.2)	0.004
Glycemia, mg/dL	104.1 (17.4)	116 (35.8)	0.002
Albumin, g/dL	4.31 (0.34)	4.39 (0.26)	0.018
L1–L4 BMD, g/cm ²	0.905 (0.186)	1.015 (0.194)	<0.001
Femoral neck BMD, g/cm ²	0.638 (0.123)	0.762 (0.137)	<0.001
Total femur BMD, g/cm ²	0.777 (0.128)	0.945 (0.140)	<0.001
Fat mass, kg	11.9 (4.7)	17.6 (5.8)	<0.001

The values are expressed as mean (SD) or percentage

^a Mann–Whitney test for continuous variables; Fisher's exact test, Chi-square, and test likelihood ratio for categorical variables

classified as sarcopenic by both methods. Fifty-one individuals had discordant sarcopenia classification by the two methods, of those 38 men were considered sarcopenic only by ASM adjusted for fat criteria, and 13 men were classified as sarcopenic by ASM/height² definition and not by ASM adjusted for fat criteria. The distribution of subjects according to the presence or absence of sarcopenia, using each method, is shown in Fig. 1.

Sarcopenia and body mass index classification

Using ASM/height² and ASM adjusted for fat sarcopenia criteria, 68.5 % (37/54) versus 32.9 % (26/79) (*p*<0.001)

Table 2 Demographic, clinical, and laboratorial data in older men with and without sarcopenia classified by the ratio of appendicular skeletal mass (ASM) adjusted for fat

Variables	Sarcopenia		<i>p</i> value ^a
	Yes <i>N</i> =79	No <i>N</i> =320	
Age, years	74.2 (5.7)	72.3 (4.8)	0.007
Black race, %	17.7	32.8	0.009
Height, cm	162.9 (7.0)	162.5 (7.5)	0.678
Weight, kg	64.7 (11.0)	71.4 (12.5)	<0.001
BMI, kg/m ²	24.4 (4.0)	26.9 (3.9)	<0.001
Alcohol, %	10.1	8.4	0.635
Alcohol, U/day	10.0 (18.0)	6.4 (13.7)	0.078
Current smoking, %	29.1	11.3	<0.001
Low physical activity, %	25.3	9.06	<0.001
History of falls, %	31.6	26.3	0.335
Number of falls / year	0.70 (1.7)	0.43 (0.97)	0.330
Fragility fractures, %	13.9	6.6	0.031
Diabetes mellitus, %	13.9	17.5	0.446
Arterial hypertension, %	57	55.6	0.830
Cardiovascular event, %	17.7	15.9	0.701
Calcium intake, mg	423.0 (301.0)	396.3 (320.4)	0.349
Alkaline phosphatase, U/L	190.6 (89.0)	172.0 (61.3)	0.173
25 OHD, ng/mL	21.4 (10.3)	21.2 (9.5)	0.778
eGFR, mL/min	54.0 (20.6)	60.2 (17.4)	<0.001
LDL-C, mg/dL	118.2 (36.3)	116.1 (34.0)	0.691
HDL-C, mg/dL	52.6 (12.5)	52.4 (13.3)	0.663
Triglycerides, mg/dL	150.5 (208.0)	131.2 (78.1)	0.808
Glycemia, mg/dL	108.5 (35.0)	116 (33.8)	0.005
Albumin, g/dL	4.35 (0.31)	4.39 (0.27)	0.148
L1–L4 BMD, g/cm ²	0.959 (0.195)	1.011 (0.196)	0.024
Femoral neck BMD, g/cm ²	0.679 (0.134)	0.761 (0.138)	<0.001
Total femur BMD, g/cm ²	0.836 (0.147)	0.943 (0.142)	<0.001
Fat mass, kg	17.3 (7.2)	16.7 (5.7)	0.644

The values are expressed as mean (SD) or percentage

^a Mann–Whitney test for continuous variables; Fisher's exact test, Chi-square, and test likelihood ratio for categorical variables

were underweight, and 5.5 % (3/54) versus 27.8 % (22/79) (*p*=0.001) were overweight/obese, respectively.

Further analysis, assessing exclusively discordant data, revealed that of those 13 subjects classified as sarcopenic only by ASM/height², 84.6 % (11/13) were underweight and solely one (7.7 %) was considered overweight/obese. In contrast, of those 38 older men classified as sarcopenic only by ASM adjusted for fat criteria, none of them were underweight and 53 % (20/38) were overweight/obese.

Of the 50 subjects considered underweight, 52 % (26) were considered sarcopenic by ASM adjusted for fat criteria and 74 % (37) by ASM/height², being 22 % (11) classified as

Fig. 1 Distribution of individuals according to the two sarcopenia criteria. The x-axis represents the ASM/h^2 criteria and values equal or lower than 7.26 define sarcopenic men (gray color). The y-axis represents the ASM adjusted for fat and residuals lower than -2.06 define sarcopenic men (vertical lines)

sarcopenic only by $ASM/height^2$ and not by ASM adjusted for fat criteria.

Risk factors according to $ASM/height^2$ and ASM adjusted for fat mass criteria

Regarding to risk factors, sarcopenia by $ASM/height^2$ criteria was associated, in univariate analysis, with lower weight ($p<0.001$), lower BMI ($p<0.001$), higher frequency of current smoking ($p<0.001$), higher frequency of low physical activity ($p<0.001$), higher frequency of fragility fractures ($p=0.005$), higher alkaline phosphatase ($p=0.017$), lower eGFR ($p<0.001$), higher HDL-C ($p=0.014$), lower triglycerides ($p=0.004$), lower glycemia ($p=0.002$), lower albumin ($p=0.018$), lower bone density parameters (L1 L4 BMD, femoral neck BMD, and total femur BMD, $p<0.001$), and lower fat mass ($p<0.001$). No difference was observed regarding biochemical [calcium: 9.3 (0.43) vs. 9.3 (0.45), $p=0.915$; phosphorus: 3.24 (0.55) vs. 3.11 (0.50), $p=0.079$] and hormones (25OHD: 20.6 (10.8) vs. 21.3 (9.4), $p=0.549$; PTH: 42.8 (28.3) vs. 36.96 (16.16), $p=0.432$) bone parameters comparing sarcopenic versus non-sarcopenic men.

Concerning ASM adjusted for fat criteria, the individuals considered sarcopenic were older ($p=0.007$), with lower frequency of Black race ($p=0.009$), lower weight ($p<0.001$), lower BMI ($p<0.001$), higher frequency of current smoking ($p<0.001$), higher frequency of low physical activity ($p<0.001$), higher frequency of fragility fractures ($p=0.031$), lower eGFR ($p<0.001$), lower glycemia ($p=0.005$), and lower bone density parameters (L1 L4 BMD, femoral neck BMD, and total femur BMD, $p<0.05$). No difference was observed regarding biochemical [calcium: 9.3 (0.41) vs. 9.3 (0.46), $p=0.374$; phosphorus: 3.22

(0.52) vs. 3.10 (0.50), $p=0.069$] and hormones (25OHD: 21.4 (10.3) vs. 21.2 (9.5), $p=0.778$; PTH: 40.0 (23.4) vs. 37.23 (16.9), $p=0.501$) bone parameters.

Logistic regression analysis was performed using parameters that showed statistical significance in the univariate analysis for both criteria, and BMD or T-scores were analyzed separately to the regression analysis. Regarding $ASM/height^2$ criteria, the best logistic regression model revealed that sarcopenia was associated with age ($p=0.05$), BMI ($p<0.001$), Black race ($p=0.03$), current smoking ($p=0.02$), physical activity ($p=0.04$), and total femur BMD ($p=0.04$) in community-dwelling older men. In ASM adjusted for fat criteria, the best logistic regression analysis found the same variables associated with sarcopenia: age ($p=0.03$), BMI ($p=0.001$), Black race ($p=0.002$), current smoking ($p=0.003$), physical activity ($p=0.006$), and total femur BMD ($p=0.01$) (Table 3). The assumptions required for linear regression models were fitted at final model.

Discussion

Our study demonstrated that the criteria based on ASM adjusted for fat identify a greater number of older sarcopenic men, although $ASM/height^2$ criteria should be used in underweight subjects. Nevertheless, the risk factors for this syndrome were similar comparing the two criteria.

The advantage of this study is to include a well-characterized sample of older adults, a population known to have the highest prevalence of sarcopenia [11, 28–31]. Actually, the analysis of older and younger individuals simultaneously may hinder interpretation of risk [29–31], since they are age-related factors. Furthermore, the community-dwelling

Table 3 Variables included in the best logistic regression model according to ASM/height² and ASM adjusted for fat sarcopenia criteria in older men

Variables	Sarcopenia	
	OR (95 % CI)	
	ASM/height ² criteria	ASM adjusted for fat criteria
Age	1.08 (1.00–1.18)	1.05 (1.00–1.11)
BMI	0.45 (0.36–0.57)	0.86 (0.79–0.94)
Black race	0.27 (0.08–0.88)	0.31 (0.14–0.65)
Current smoking	3.44 (1.18–9.96)	2.83 (1.40–5.74)
Physical activity	0.28 (0.08–0.95)	0.35 (0.16–0.75)
Total femur BMD	0.019 (0.0003–0.98)	0.06 (0.007–0.65)

Data are expressed as odds ratios (OR) and 95 % confidence intervals (CI)

healthy individuals' analysis minimizes confounding variables, particularly those observed in institutionalized individuals [32, 33]. The study design including only men represents another important characteristic of this work, since it is well known that sarcopenia differs strongly according to gender, regarding prevalence, risk features, and outcomes [6, 11, 30–32]. Moreover, the WHO classification, the most widely used BMI categorization, is not the most adequate criteria to classify older adults, due to the increased relative body fat with age, making this measure prone to systematic misclassification. Therefore, the BMI classification adjusted by age used in our work further strengthens our findings.

The present data showed that the sarcopenia definition according to ASM adjusted for fat criteria seems to be more appropriate for identifying sarcopenia in older men, since the prevalence of overweightness/obesity was high, reaching almost 50 % of our sample. According to the literature, the prevalence of obesity in older adults appears to be increasing in most developed and developing countries [34]. In fact, in a US survey, the prevalence of obesity was 22.9 % in 60- to 69-year olds and 15.5 % in those older than 70, representing a 56 and 36 % increase, respectively, from 1991 prevalence data [35]. This prevalence trends may be slightly lower in parts of Europe, where 22 % of woman and 12 % of men older than 75 are reportedly obese and there seems to be geographic variation [36]. A study in the Mexican population also showed that this frequency is increased with 20.9 % of the older population considered obese [37].

In this context, sarcopenia classification adjusted by fat seems to be more useful than the ASM/height² criteria. In fact, comparable to our findings in men, in a study of 189 healthy, White, postmenopausal women using DXA and ASM/m², 25.9 % were classified as sarcopenic. They identified sarcopenia in 36.7 % of thin women but only 9.2 % in overweight women and none in obese women. When they applied the ASM adjusted for fat mass criteria, 8.5 % of thin women were classified as sarcopenic, but 40 % of overweight

women, and 85.7 % of obese women were classified as sarcopenic [38].

Moreover, an equation based on the linear regression models was developed to allow the analysis of the expected ASM according to total fat mass. The result obtained from this formula should be subtracted from the ASM obtained by DXA, and this result is the residual of the ASM. In our population, if this residual is less than −2.06, we considered the man as sarcopenic. Thus, this equation can be applied to Brazilian men aged over 65 years with BMI >22 kg/m², with a residual less than −2.06 for the sarcopenia cutoff point.

On the other hand, since none of underweight man was classified as sarcopenic by only ASM adjusted for fat, and almost a quarter of them were considered sarcopenic only by ASM/m², the present study demonstrated that this former criteria seems to be the best method to recognize sarcopenia in thin men. Thus, as our sample is representative of the Brazilian older population according to the Brazilian Institute of Geography and Statistics [39]; as previously reported by our group [12, 15, 40], the sarcopenia assessment by ASM/height² method should be considered in Brazilian older men with BMI <22 kg/m², classified as underweight according to BMI adjusted for age. Likewise, in Asian population as Japanese and Chinese, sarcopenia was classified according to ASM/height² method and underweight was considered a strong risk factor for these individuals [41, 42].

Sarcopenia has been linked to a number of morbid outcomes in older adults such as falls, fractures, and physical disability, being related to increasing of mortality [2–4, 43]. Interestingly, in our study, no association between sarcopenia and falls was observed, although fragility fractures were more frequent in older sarcopenic men. The possible explanation for this finding could be that a decrease of muscle mass is associated with bone structure compromising such as narrower bones and thinner cortices [44]. In fact, other authors also did not show an association between sarcopenia and lower extremity performance [45].

In the final regression analysis, similar risk factors were observed for both criteria. As expected, a positive association with BMI, Black race, physical activity, and BMD with skeletal mass was found and they were considered as protective parameters for sarcopenia [30, 34, 42, 46]. In contrast, current smoking and age were risk factors for sarcopenia among community-dwelling older men, as reported previously [30, 42]. No difference was observed concerning calcemic hormones in both sarcopenia criteria, even for 25OH vitamin D status, that has been associated with muscle involvement [31].

This study identified the risk factors for sarcopenia in community-dwelling older men and provides novel evidence that the optimal criteria should be selected according to BMI: ASM adjusted for fat for the majority older community-dwelling men, except those classified as underweight, for whom the ASM/height² criteria is more appropriate.

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Conflicts of interest None.

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From: em@editorialmanager.com
To: dsdomiciano@hotmail.com
Date: Wed, 3 Sep 2014 11:12:54 -0400
Subject: - Please verify if you are a co-author

Re: "Persistent hypovitaminosis D and loss of hip bone mineral density over time as additional risk factors for recurrent falls in a population-based prospective cohort of elderly persons living in the community. The São Paulo Ageing & Health (SPAH) Study."
Full author list: Ketty Lysie Libardi Lira Machado, MD; Diogo Souza Domiciano, MD; Luana Gerheim Machado, MD; Jaqueline Barros Lopes, MD, PhD; Camille Pinto Figueiredo, MD, PhD; Liliam Takayama; Ricardo M Oliveira, MD; Paulo Rossi Menezes, MD, PhD; Rosa Maria Rodrigues Pereira, MD, PhD

Dear Dr Diogo Domiciano,

We have just received the submission entitled: "Persistent hypovitaminosis D and loss of hip bone mineral density over time as additional risk factors for recurrent falls in a population-based prospective cohort of elderly persons living in the community. The São Paulo Ageing & Health (SPAH) Study." for possible publication in Osteoporosis International, and you are listed as one of the co-authors.

The manuscript has been submitted to the journal by Dr. Prof. Rosa Maria Rodrigues Pereira who will be able to track the status of the paper through his/her login.

If you have any objections, please contact the editorial office as soon as possible. If we do not hear back from you, we will assume you agree with your co-authorship.

Thank you very much.

With kind regards,

Springer Journals Editorial Office
Osteoporosis International

Apêndice C - Prêmios

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**DIOGO SOUZA DOMICIANO, LUANA GERHEIM MACHADO, JAQUELINE BARROS LOPES,
CAMILLE PINTO FIGUEIREDO, VALERIA CAPARBO, LILIAM TAKAYAMA, PAULO ROSSI
MENEZES, RICARDO OLIVEIRA, ROSA MARIA RODRIGUES PEREIRA**

Pelo trabalho: **INCIDÊNCIA E FATORES DE RISCO PARA FRATURA VERTEBRAL POR
OSTEOPOROSE EM IDOSOS BRASILEIROS DA COMUNIDADE: SÃO PAULO AGEING &
HEALTH STUDY (SPAHE)**

Pernambuco, 26 de outubro de 2013

João Lindolfo Cunha Borges
Presidente da ABRASSO

Vera Lucia Szejnfeld
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Francisco Bandeira
Presidente da Comissão Científica

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DIOGO SOUZA DOMICIANO, LUANA GERHEIM MACHADO, CAMILLE PINTO
FIGUEIREDO, JAQUELINE BARROS LOPES, LILIAM TAKAYAMA, VALERIA CAPARBO,
MÁRCIA SCAZUFCA, ROSA MARIA RODRIGUES PEREIRA

Pelo trabalho: **BAIXA DENSIDADE MINERAL ÓSSEA E MAIORES NÍVEIS DE PARATORMÔNIO: PREDITORES INDEPENDENTES DE MORTALIDADE EM INDIVÍDUOS IDOSOS DA COMUNIDADE. SÃO PAULO AGEING & HEALTH STUDY (SPAH)**

Pernambuco, 26 de outubro de 2013

João Lindolfo Cunha Borges
Presidente da ABRASSO

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Diretoria Científica da ABRASSO

Francisco Bandeira
Presidente da Comissão Científica

Certificamos que o trabalho **Incidência e fatores de risco para fratura vertebral por Osteoporose em idosos brasileiros da comunidade: estudo prospectivo de base populacional - São Paulo Ageing & Health Study (SPAH)**, dos autores: Diogo S Domiciano, Luana G Machado, Jaqueline B Lopes, Camille P. Figueiredo, Valéria F Caparbo, Liliam Takayama, Ricardo M Oliveira, Paulo R Menezes e Rosa Maria R. Pereira é o vencedor do Prêmio Jovem Pesquisador concedido durante o XXX Congresso Brasileiro de Reumatologia.

Mittermayer Barreto Santiago
 Diretor Científico da Sociedade
 Brasileira de Reumatologia

Claudia Diniz Lopes Marques
 Diretora Científica do XXX Congresso
 Brasileiro de Reumatologia

Walber Pinto Vieira
 Presidente da Sociedade
 Brasileira de Reumatologia

Angela Luzia Branco P. Duarte
 Presidente do XXX Congresso
 Brasileiro de Reumatologia

CERTIFICADO

Certificamos que o trabalho CO.03-“Baixa densidade mineral óssea e maiores níveis de paratormônio: preditores independentes de mortalidade em indivíduos idosos da comunidade. São Paulo Ageing & Health Study (SPAH)” de autoria de **Domiciano DS, Machado LG, Lopes JB, Figueiredo CP, Caparbo V, Takayama L, Menezes PR, Pereira RMR** recebeu o **1º lugar no Prêmio Jovem Investigador** no XX Encontro de Reumatologia Avançada, realizado de 27 a 29 de março de 2014 em São Paulo, SP.

Dawton Y. Torigoe
Presidente SPR

Simone Appenzeller
Diretora Científica