Fatores associados à elevada densidade mineral óssea em mulheres

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Dedico esta tese

Aos ***meus avós*** *in memorium, sempre presentes em meu coração.*

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"O fato é que ciência e sabedoria são coisas muito diferentes.
Ciência é conhecimento do mundo. Sabedoria é conhecimento da vida."

Rubem Alves

Acredito que o verdadeiro cientista deva associar a exuberância do conhecimento científico à grandiosidade da sabedoria.

RESUMO

Sarkis KS. Fatores associados à elevada densidade mineral óssea em mulheres [tese de doutorado]. São Paulo: Faculdade de Saúde Pública; 2012.

Introdução: Vários parâmetros estão associados com alta densidade mineral óssea (DMO), como obesidade, etnia negra, atividade física intensa, padrão alimentar e alguns medicamentos. **Objetivos:** avaliar a prevalência e os principais aspectos associados com a DMO elevada em mulheres saudáveis. **Métodos:** Em revisão do banco de dados de DMO realizadas na área metropolitana de São Paulo, a alta DMO (acima de 1400 g/cm^2 em coluna lombar e / ou acima de 1200 g/cm^2 em colo do fêmur) foi encontrada em 421 exames de um total de 21000 exames avaliados. Após os critérios de exclusão permaneceram no estudo 40 mulheres com DMO elevada e pareadas com 40 mulheres com DMO normal, para cor de pele, peso, idade e estado menopausal. A história médica, a ingestão de alimentos e AF foram avaliadas por meio de questionários validados. Para a avaliação do padrão alimentar os alimentos foram agrupados segundo a semelhança nutricional. A composição corporal foi avaliada por meio de densitometria óssea com raio X duo-energético (DXA - *GE Lunar Radiation Corporation*, model DPX, Madison, WI, USA). Radiografia da coluna torácica e lombar foram realizadas para excluir alterações degenerativas ou fraturas. Os parâmetros bioquímicos incluíram tanto os perfis hormonais e lipídicos, como marcadores bioquímicos do metabolismo mineral e ósseo. A análise estatística incluiu testes paramétricos e não paramétricos, modelos de regressão linear e análise fatorial. $P < 0.05$ foi considerado significante. **Resultados:** A idade média foi de 50.9 (8.3) anos. Houve diferença significante entre os grupos em relação à massa magra (massa magra total, $p=0.029$ e massa magra apendicular, $p = 0.007$), sendo maior no grupo com DMO elevada, e em relação ao C-telopeptídeo de colágeno tipo I (CTX), que foi inferior no grupo DMO elevada ($p = 0.04$). No modelo final de regressão multivariada, a menor ingestão de gordura e gordura corporal, bem como menor concentração de LDL-colesterol previu aproximadamente 35% da DMO elevada nas mulheres (R2 ajustado = 0.347, $p < 0.001$). Além disso, maiores quantidades de massa magra e concentrações séricas de IGF-1 exerceram papel de proteção, independente da idade e peso. Com relação ao padrão dietético, as mulheres com DMO elevada apresentaram uma dieta saudável com baixo consumo de carnes processadas. **Conclusão:** Os resultados demonstram o potencial

efeito deletério de componentes relacionados ao metabolismo lipídico como a ingestão de gordura e gordura corporal e maior concentração de LDL sobre a massa óssea e metabolismo em mulheres com DMO elevada além de evidenciar que as mulheres com elevada DMO apresentam alimentação mais saudável em relação ao grupo controle avaliado.

Descritores: Densidade mineral óssea, Composição corporal, Metabolismo lipídico, Dieta, Metabolismo mineral, Mulheres e Padrão alimentar

ABSTRACT

Sarkis SK. Factors associated with high bone mineral density in Brazilian women [thesis]. São Paulo: Faculdade de Saúde Pública; 2012.

Introduction: Several factors are associated with high bone mineral density (BMD), such as overweight, race (african descendent), intense physical activity (PA), dietary patterns and some medications. **Objectives:** the aim of the study was to evaluate the prevalence and the main aspects associated with high BMD in healthy women. **Methods:** Considering data on BMD from the São Paulo metropolitan area database, the high BMD (over 1400 g/cm^2 at lumbar spine and/or above 1200 g/cm^2 at femoral neck) was found in 421 exams. After the exclusion criteria, 40 women in the study remained with high BMD compared to 40 healthy women with normal BMD, paired together in relation to weight, age, skin color and menopausal status. Medical history, food intake and PA were assessed through validated questionnaires. Foods were systematically grouped together on the basis of similarities of food and nutrient composition and entered into factor analysis. Body composition was evaluated through a DXA (*GE Lunar Radiation Corporation*, model DPX, Madison, WI, USA). Radiography of the thoracic and lumbar spine was carried out to exclude degenerative alterations or fractures. Biochemical parameters included both lipid and hormonal profiles, along with mineral and bone metabolism. Statistical analysis included parametric and nonparametric tests, linear regression models and factor analysis. $P < 0.05$ was considered significant. **Results:** The mean age was 50.9 (8.3) years. There were significant differences between groups in relation to lean body mass (total fat-free mass, p=0.029 and appendicular lean mass, p = 0.007), being higher in women with high BMD and serum C-telopeptide of type I collagen (CTX), and was lower in the high BMD group ($p = 0.04$). In the final model of multivariate regression, a lower fat intake and body fatness as well as a lower concentration of LDL-cholesterol predicted almost 35% of high BMD in women, (adjusted R2 = 0.347; $p < 0.001$). In regards to dietary patterns, women with high BMD showed a healthy diet with low consumption of processed meats. **Conclusion:** Our results demonstrated the deleterious potential effect of lipid metabolism-related components including fat intake, body fat and higher lipid profile on bone mass and metabolism in women with high BMD, along with showing that women with high BMD have a healthier diet.

Descriptors: Bone mineral density, Body composition, Lipid metabolism, Diet, Mineral metabolism, Women, Dietary Pattern

ÍNDICE

Anexo II- Questionário sobre fatores de risco da massa óssea
Anexo III- Questionário de Frequência Alimentar
Anexo IV- Questionário sobre atividade física
Anexo V - Aprovação do comitê de ética

LISTA DE TABELAS E FIGURAS

Artigo 1

Artigo 2

Artigo 3

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

25(OH)D3	*Calcidiol*
ACSM	*American College Sports of Medicine*
ANOVA	*Análise de variância*
BRAZOS	*Brazilian Osteoporosis Study*
BMD	*Bone Mineral Density*
BMI	*Body mass index*
COEP	*Comitê de ética em pesquisa*
CTX	Telopeptídeo carboxiterminal do colágeno tipo I
DMO	Densidade Mineral Óssea
DP	Desvio padrão
DRIs	Dietary Reference Intake
DXA	Dual energy x-ray absorptiometry
EDMO	Elevada Densidade Mineral Óssea
FFQ	Food Frequency Questionnaire
FIFI	Fundação Instituto de Diagnóstico por Imagem
FSH	Hormônio folículo estimulante
FSP	Faculdade de Saúde Pública
GH	Hormônio do crescimento
GnRH	Hormônio liberador de gonadotrofina
HBD	High bone density
IGFBP-1	Proteína 1 de ligação ao fator de crescimento semelhante à insulina
IGF-1	Fator de crescimento semelhante a insulina
IL-6	Interlecina -6
IMC	Índice de Massa Corporal
IOM	*Institute of Medicine*
LH	Hormônio luteinizante
NTX	N-telopeptídeo do colágeno tipo I
OMS	Organização Mundial da Saúde
OP	Osteoprotegerina
P1NP	N-terminal propeptideo de procolágeno tipo 1
PC	Principal Component

PTH	Paratormônio
rhPTH 1-34	PTH recombinante humano 1-34 (teriparatida)
QFA	Questionário de Frequência alimentar
RANK	Receptor do Ativador Nuclear Kβ
RANK-L	Ligante do Receptor do Ativador Nuclear Kβ
ROI	Oxigênio Intermediário Reativo
ROS	Espécies reativas de oxigênio
SHBG	Globulina ligadora dos hormônios sexuais
SPSS	*Statistical Package for the Social Sciences*
TNF-α	Fator de necrose tumoral alfa
USP	Universidade de São Paulo
%	Porcentagem
>	Maior
<	Menor
≥	Maior ou igual
≤	Menor ou igual
µ	Micro

1.APRESENTAÇÃO

Esta tese inicia-se com a seção de introdução, seguida dos objetivos, metodologia, resultados, considerações finais e, por fim, dos anexos. Na seção de resultados encontram-se três artigos, sendo dois aceitos para publicação e um a ser submetido ao periódico para a publicação. O primeiro manuscrito é uma revisão da literatura e os dois últimos são compostos dos seguintes tópicos: introdução, metodologia, resultados, discussão, referências bibliográficas, tabelas e gráficos.

2.INTRODUÇÃO

2.1 ELEVADA DENSIDADE MINERAL ÓSSEA

A ocorrência de Elevada Densidade Mineral Óssea (EDMO) tem sido descrita na literatura na última década. Porém, como a maioria dos estudos investiga indivíduos com baixa Densidade Mineral Óssea (DMO), os critérios diagnósticos para osteoporose já estão bem estabelecidos pela Organização Mundial da Saúde (OMS, 1994), mas o mesmo não ocorre com a EDMO.

Em relação à mensuração da DMO, realizada pela densitometria óssea com raio X duo-energético (DXA), os indivíduos que apresentam valores de T-score igual ou acima de -1 desvio padrão (DP) são classificados com massa óssea normal; já, indivíduos abaixo deste valor são classificados como tendo osteopenia (T-score entre -1.0DP e -2.5DP) ou osteoporose (T-score igual ou menor que -2.5DP), dependendo do valor do T-score. Esta classificação é reconhecidamente aceita, porém não há um valor de T-score limítrofe para a classificação da massa óssea acima do normal (WHO, 1994; ISCD, 2006; NOF, 2008).

Partindo do pressuposto de que valores de T-score menores ou iguais a -2.0 DP indicam baixa densidade óssea e um maior risco de fratura, seria aceitável a utilização de valor de T-score 2.0 DP como ponto de corte para classificar a massa óssea acima do normal.

Apesar de não haver um ponto de corte consensual para EDMO, estudo de coorte realizado por PESONEM e cols. (2005), com mais de 1800 mulheres, sugere que o ponto de corte para elevada DMO seja de 1,209 g/cm^2 para o colo do fêmur e 1,228 g/cm^2 para a coluna lombar (quartis superiores). Avaliando mais de 96 mil exames de densitometria óssea, GREGSON e cols. (2009), definiram valores de Z-escore, igual ou maior do que 3,5DP para a coluna vertebral e / ou colo do fêmur para a caracterização de tais indivíduos; com base neste critério, apenas 169 indivíduos com alta densidade óssea foram encontrados (aproximadamente 0,2% do total amostra).

Poucos estudos abordam a prevalência ou os principais aspectos clínicos e laboratoriais de indivíduos com EDMO. No entanto, a maioria deles aponta que peso elevado (ORXOLL e cols., 2000) e índice de massa corpórea (IMC) acima de 30

kg/m^2 (WHYTE, 1997; ORXOLL e cols., 2000; CHEN e cols., 2002), fatores genéticos como mutações no gene da proteína 5 relacionada com o receptor do LDL - LRP5 (WHO, 1998; VAN WESENBEECK e cols., 2003; CUI e cols., 2011), sexo masculino, etnia negra (BELL, 1997), atividade física regular (LORD e cols., 1996.; SILMAN e cols., 1997), ingestão elevada de cálcio (acima de 1500 mg/ dia) (HEANEY e cols., 1978; HEANEY e cols., 1989; KANIS,1989), assim como o uso de medicações como estatinas (PASCO e cols., 2002; CHUENGSAMARN e cols. 2010) e diuréticos tiazídicos (TANAKA e cols., 2001; KAMEL, 2002; OLMOS e cols., 2010) parecem exercer influência positiva sobre a densidade óssea.

Além disso, sabe-se que indivíduos obesos; pacientes com câncer de mama e endométrio, com receptor estrogênico positivo (CAULEY e cols., 1996; CHEN e cols., 2008; GREINER e cols., 2010); diabéticos tipo II (WHYTE e cols., 2000; MA e cols.,2012) e atletas (ALFREDSON e cols., 1996; ALFREDSON e cols., 1998; TRUTSCHNIGG e cols., 2008) apresentam maior densidade óssea do que indivíduos saudáveis; porém, os fatores determinantes da EDMO ainda não estão bem estabelecidos (WHYTE, 1997; PESONEM e cols., 2005).

Outro ponto obscuro se deve ao risco de fraturas. Não se sabe se indivíduos com EDMO apresentam menor risco de fratura, já que tais valores de DMO podem associar-se a uma diminuição da resistência mineral óssea, uma vez que EDMO pode não estar relacionada à resistência óssea (CHAVASSIEUX e col, 2007).

A seguir serão descritos os principais fatores não genéticos que interferem na DMO

2.2 ANTROPOMETRIA E COMPOSIÇÃO CORPORAL

Os mecanismos relacionados ao aumento da DMO advindos dos fatores antropométricos e composição corporal ainda não estão totalmente elucidados, porém, sugere-se que valores de Índice de Massa Corporal (IMC) representem uma importante proporção na variação da DMO (8,9 – 19,8%) (FELSON e cols., 1993; REID, 2002).

MORIN e LESLIE (2009), em estudo de coorte retrospectivo realizado em 16.500 mulheres acima de 50 anos, relatam ser incomum mulheres com EDMO

(0,9%), no entanto, uma maior frequência (43,5%) foi observada nas que apresentam valores de IMC acima de 30 kg/m^2 , indicando uma forte correlação entre EDMO e elevados valores de IMC.

O IMC indica a adequação do peso do indivíduo (em kg) para a sua altura (em metros quadrados) (OMS, 1995), assim, a avaliação realizada pelo IMC restringe-se ao peso de uma maneira geral não havendo diferenciação entre seus componentes: massa magra e massa gorda (LEKAMWASAM e cols., 2009).

Estudos mostram que, além do peso, a massa magra e massa gorda apresentam impacto sobre o osso de maneiras distintas (TAKADA e col, 1997; ILICH e cols., 2002; GINTY, 2005; REID e cols., 2006; REID e cols., 2008; PARK e cols., 2012; LEE, 2012).

O aumento da massa magra ocasiona aumento da força muscular e, assim, estimula o remodelamento ósseo por meio do efeito do estresse mecânico (TAKADA e col, 1997). Este efeito parece ser decorrente da ação direta da "carga mecânica" sobre o osso exercido pela força e massa muscular, estimulando o esqueleto (ILICH e col, 2002). De acordo com a maioria dos autores, representa o principal determinante da densidade óssea (ILCHI e cols. 2002; GENARO e cols., 2009; PARK e cols., 2012; LEE, 2012).

A massa adiposa contribui de modo menos relevante. Especula-se que um dos principais mecanismos fisiopatológicos se deva ao aumento das concentrações séricas de leptina, hormônio secretado pelos adipócitos, que parece agir de forma direta no esqueleto, regulando o desenvolvimento dos osteoclastos, reduzindo a produção de Receptor do Ativador Nuclear Kβ (RANK) e do Ligante do Receptor do Ativador Nuclear Kβ (RANK-L), aumentando a Osteoprotegerina (OP) e resultando em uma inibição da osteoclastogênese. Sua atuação também ocorre de maneira central, via hipotálamo, porém, esta ação, ao contrário da descrita anteriormente, suprime a formação óssea (BORBA e cols., 2003; REID e cols., 2006; REID, 2008).

Além disso, em obesos, ocorre aumento da secreção de hormônios pancreáticos (insulina, preptina e amilina), que atuam positivamente sobre o tecido ósseo. A condição hiperinsulinêmica, associada à maior quantidade de tecido adiposo, resulta em algumas anormalidades, tais como, elevada produção ovariana de estrogênios e reduzida síntese hepática de proteínas ligantes de hormônios sexuais. A

amilina é secretada juntamente com a insulina e inibe a reabsorção óssea, enquanto a preptina aumenta a atividade dos osteoblastos, especialmente em obesos (REID, 2008).

Outro hormônio envolvido é a grelina, sintetizada em sua maior parte no estômago. Há evidências de que seu efeito no tecido ósseo seja duplo: os receptores encontram-se nos osteoblastos que agem estimulando a proliferação e diferenciação dos mesmos (FUKUSHIMA e cols., 2005; MACCARINELLI e cols., 2005), porém, apresenta ação na osteoclastogênese acompanhada de jejum. Os resultados em humanos ainda são contraditórios (REID, 2008).

2.3 ETNIA

Mulheres negras apresentam maior densidade mineral óssea quando comparadas com as brancas (ALOIA e cols.,1999), principalmente em sítios como o colo do fêmur e quadril (CHANTLER e cols., 2012). A maior reabsorção renal de cálcio e resistência à ação reabsortiva do PTH é um dos principais mecanismos propostos (KLEEREKOPER e cols., 1994). Além disso, a maior massa muscular das negras, devido à maior modulação muscular por tração (força biomecânica), também deve ser considerada, resultando em menor risco de fraturas em ambos os sexos (BARON e cols., 1994; LAUDERDALE e cols., 1998; JACOBSEN e cols., 1992; HEANEY, 1995).

2.4 ATIVIDADE FÍSICA

Os benefícios da atividade física para a massa óssea têm sido amplamente reconhecidos (MARCUS, 1998). Os prováveis mecanismos envolvem a contração muscular, que proporciona um aumento das fibras musculares e contribui para o aumento da massa óssea (MATSUDO, e cols. 2000). O impacto proporcionado pelo exercício na massa óssea, gerando uma resposta osteogênica mecânica adaptativa; liberação de hormônios anabólicos, como o hormônio do crescimento (GH), fator de crescimento semelhante a insulina (IGF-1), estrógeno e o paratormônio (PTH), que promovem sinais para a resposta osteogênica (BORER, 2005). Adicionalmente, o

efeito piezoelétrico, explicado pelas ações mecânicas que geram diferenças no potencial elétrico dos ossos, e agem como um campo elétrico, estimula a atividade celular, levando à deposição de minerais nos pontos de estresse (LANYON e HARTMAN apud CADORE e cols., 2005).

Esses aspectos são demonstrados em estudos onde há incremento de marcadores de formação óssea, como da osteocalcina e do P1NP, decorrentes da atividade física (ADAMI e cols., 2008) e em maior densidade óssea em atletas de modalidades esportivas de alta intensidade, resistência e impacto, (ALFREDSON e cols., 1996; ALFREDSON e cols., 1998; TRUTSCHNIGG e cols., 2008, MORGAN e cols., 2011).

Em mulheres na pré e pós-menopausa há resultados contraditórios, de acordo com o tipo de treinamento utilizado. (BASSEY e cols., 1998).

WALLACE e CUMMING (2000), em artigo de revisão, demonstram efeitos positivos da atividade física (exercícios com e sem impacto, em especial corrida e musculação, respectivamente, sobre a densidade óssea vertebral). O mesmo é encontrado em meta-análise realizada por MARTYN e CARROL (2010), na qual concluem que exercícios de impacto associados aos de resistência apresentam efeito positivo. Por outro lado, atividades aquáticas, como natação e hidroginástica, não exerçam benefícios consistentes para a saúde óssea (EMSLANDER e cols., 1998).

O efeito do exercício em indivíduos não atletas parece não ocorrer a curto prazo, no entanto, acredita-se ser substancial se acumulado ao longo dos anos (WALLACE e CUMMING, 2000)

Em suas posições oficiais, o *American College Sports of Medicine (ACSM)* sugere que, em adultos, o incremento da densidade óssea ocorra somente com exercícios aeróbios de alta intensidade e resistidos. A freqüência varia conforme a modalidade. Para exercícios de impacto, recomenda-se de 3 a 5 vezes por semana e para os de resistência, de 2 a 3 vezes por semana, com duração de trinta a sessenta minutos cada (ACSM, 2004).

2.5 FATORES NUTRICIONAIS

Embora existam diversas evidências sobre a associação entre micro e macronutrientes e baixa massa óssea, poucos são os estudos que relacionam o consumo dietético e elevada densidade óssea.

A seguir serão descritos alguns nutrientes, bem como padrões alimentares relacionados à DMO.

2.5.1 Proteína

Constituinte primário do osso, a proteína, apresenta efeito anabólico benéfico ao osso, especialmente se o consumo de cálcio for adequado (DAWSON-HUGHES e HARRIS, 2002).

A proteína dietética regula a produção hepática e os níveis plasmáticos do hormônio de crescimento (GH) e do IGF-1, responsável por exercer funções como diferenciação, maturação e recrutamento dos osteoblastos (BORBA, 2003). Sua restrição contribui para a diminuição plasmática deste hormônio, podendo influenciar no metabolismo ósseo, visto que o aumento do remodelamento ósseo e redução da formação óssea estão relacionados com baixos níveis plasmáticos de IGF-I (AMMANN e cols., 2000), dependente da ingestão protéica (HEANEY e cols., 1999).

Embora as dietas hipoprotéicas reduzam a densidade mineral óssea devido ao comprometimento no recrutamento e na atividade dos osteoblastos decorrentes da diminuição de IGF-1 (BOURRIN e cols., 2000), as dietas hiperproteicas apresentam resultados controversos. HUNT e cols. (2009) revelam um incremento de 27% dos valores de IGF-1 em dieta com um aumento de proteínas indicando efeito benéfico ao metabolismo ósseo. Por outro lado, estudo com dieta hiperprotéica demonstra aumento da excreção renal de cálcio, ocasionando efeito negativo na DMO (HEANEY, 1993). Este efeito parece ser minimizado quando há ingestão adequada de cálcio e de vitamina D (SCHÜRCH e cols., 1998).

2.5.2 Lipídeos

Alguns estudos encontraram associação negativa entre consumo de lipídeos e DMO (MICHAELSSON e cols., 1995; COOPER e cols., 2000; MACDONALD e cols., 2004).

Estudo em modelo animal realizado por HALADE e cols. (2010) evidencia a associação entre consumo de gorduras, obesidade e redução de massa óssea.

Sabe-se que o maior consumo de lipídeos pode comprometer a absorção do cálcio, a síntese do prostaglandinas e a osteoblastogênese (WATKINS e cols., 2003; PARHAMI e cols.,2003).

É responsável pelo aumento da oxidação do lipídeos (WATKINS e cols., 2003; PARHAMI e cols.,2003, CORWIN e cols., 2003). Além disso, está relacionada com maior expressão dos fatores de diferenciação da adipogênese, em especial os PPAR-γ (receptores ativados por proliferadores de peroxissoma gama) (INOUE e cols., 2005; YU e cols. 2003; ACKERT-BICKNELL e cols, 2008).

De acordo com os dados do *Framingham Osteoporosis Study*, o elevado consumo de gordura pode ser prejudicial para a massa óssea, particularmente em indivíduos com maior variação alélica do PPAR-γ (ACKERT-BICKNELL e cols, 2008).

2.5.3 Cálcio e Vitamina D

O cálcio é o mineral mais abundante no organismo, sendo que aproximadamente 99% encontram-se no esqueleto e o restante distribui-se nos dentes, fluídos corporais e tecidos moles (NORDIN, 1997). Está envolvido em funções biológicas como a contração muscular, mitose, coagulação sanguínea, transmissão do impulso nervoso ou sináptico e suporte estrutural do esqueleto (MILLER e cols., 2001).

O papel do cálcio no metabolismo ósseo é amplamente conhecido (MATKOVIC e cols., 2004), assim como o fato de que sua deficiência acarreta alterações na densidade mineral óssea (BROADUS, 2003).

Este mineral é necessário para maximizar o pico de massa óssea, manter a massa óssea na idade adulta e minimizar a perda decorrente da idade (MATKOVIC e cols., 2004).

A recomendação de cálcio varia conforme os estágios de vida e foram revistas e publicadass em 2010 pelo comitê do Food and Nutrition Board/ Institute of Medicine (IOM) dos Estados Unidos, sendo de 1000mg/dia para ambos os sexos entre 19 a 50 anos. Este valor é recomendado para o sexo masculino até os 70 anos. Há uma diferenciação de valores para o sexo feminino a partir dos 50 anos (1200mg/dia); portanto, a partir dos 70 anos, para ambos os sexos, a recomendação é de 1200mg de cálcio/dia (IOM 2011).

No Brasil essa ingestão pode ser bastante diversificada devido aos diferentes hábitos regionais. Apesar disto dados obtidos em uma amostra representativa do Estado de São Paulo evidenciam o baixo consumo de cálcio, segundo gênero e idade (483 mg/d para mulheres e 410 mg/d para homens) (BUENO e cols., 2008). O *Brazilian Osteoporosis Study (BRAZOS)* ao avaliar 2420 indivíduos brasileiros em 15 estados, corrobora com os dados descritos anteriormente. O consumo médio nacional diário de cálcio foi de 400mg/dia (PINHEIRO e cols., 2009).

Segundo PEREIRA e cols. (2009) os principais motivos para a baixa ingestão de cálcio pelos brasileiros se deve, provavelmente, ao elevado custo dos principais alimentos-fonte, hábitos culturais e alimentares.

Além do consumo, outro ponto que se deve considerar é a biodisponibilidade do cálcio que depende de fatores exógenos, como fitatos, oxalatos, taninos e sódio que agem de maneira negativa; dos oligossacarídeos cuja fermentação produz ácidos graxos de cadeia curta que acidificam o intestino estimulando a absorção de cálcio e de fatores endógenos como idade, condições fisiológicas e regulação hormonal (PEREIRA e cols., 2009).

Um dos fatores hormonais é a vitamina D, nutriente que funciona como pró-hormônio, apresentando a mesma estrutura molecular que os hormônios esteróides (NORMAN, 2008).

É adquirida de duas formas: via alimentação e pela exposição solar, sendo que a última é responsável por 80% a 90% dos estoques (HOLICK, 1999). A ampla

distribuição do seu receptor VDR pelo organismo amplia os efeitos benéficos em diversos tipos de células e tecidos (HOLICK, 2004. NORMAN, 2008).

Recentemente novas recomendações de vitamina D foram publicadas pelo mesmo comitê descrito anteriormente. A recomendação aumentou em 400UI/dia ou 10 µg/dia, sendo: 15µg/dia para indivíduos entre 31 e 70 anos e 20 µg/dia para indivíduos acima de 70 anos; baseada em publicações científicas consistentes, visando não só o metabolismo ósseo, mas também os efeitos extra-ósseos. (IOM, 2011). Porém, em relatório publicado pelo IOM revela que estes últimos efeitos são inconclusivos e não podem ser confiáveis, sendo necessários mais estudos para a comprovação deste efeito.

Alguns autores acreditam que estas novas recomendações permanecem aquém da necessidade real de Vitamina D para a manutenção da massa óssea e benefícios extra-osseos (HEANEY e HOLICK, 2011).

Em nosso meio, FISBERG (2005) encontrou valores de consumo de vitamina D inferior ao recomendado. A média de ingestão em mulheres acima de 51 anos foi de mulheres 3,21µg/dia. Em mulheres idosas com osteoporose o valor médio de consumo foi de 4,2µg/dia (GENARO e cols., 2006). Baixo consumo também foi encontrado pelo *BRAZOS* ao avaliar uma amostra representativa da população brasileira, a ingestão média foi de 1,86 µg/dia (PINHEIRO e cols., 2009).

Maiores detalhes sobre metabolismo da vitamina D serão descritos posteriormente no subitem "perfil hormonal".

2.5.4 Fósforo

Mineral essencial para a formação óssea, a ação do fósforo no metabolismo ósseo está relacionada com os níveis de cálcio e paratormônio (PRENTICE, 2004).

Estudo em modelo animal sugere que dietas ricas em fósforo aumenta a expressão do RNAm do RANKL ocasionando diferenciação e aumento do número de osteoclastos (KATSUMATA e cols., 2005).

Em humanos, dietas ricas em fósforo associadas ao baixo consumo de cálcio gera alterações no metabolismo do cálcio com aumento da secreção de PTH favorecendo a perda óssea (CALVO, 1990). PINHEIRO e cols. (2009) confirmam isto ao demonstrarem que a cada 100g de fósforo consumido o risco de fratura

aumenta em 9%. Deve-se considerar que este efeito parece ocorrer apenas em dietas com baixo conteúdo de cálcio (BIZIK, 1996).

No entanto, é importante salientar que dietas restritas em fósforo não promovem ganho de DMO, mas podem ocasionar balanço negativo de fósforo e, assim, maior perda óssea. Desse modo, o adequado consumo de fósforo e cálcio é essencial para a mineralização óssea.

2.5.5 Padrão alimentar

A avaliação de nutrientes ou alimentos de maneira individual pode não ser a maneira mais adequada, uma vez que os indivíduos consomem dietas consistindo de uma variedade de alimentos com complexas combinações de nutrientes, ao inves de nutrientes isolados (OKUBO e cols., 2006). Diante disto os padrões alimentares, método que explora os múltiplos componentes dietéticos, estão sendo utilizados em inúmeros estudos.

Os padrões alimentares têm sido descritos associados com algumas doenças crônicas, incluindo doenças cardiovasculares e diabetes (KANT, 2004), mas poucos estudos têm investigado o impacto da padrões alimentares específicos na saúde óssea.

Um estudo de coorte, no Canadá, demonstrou que um padrão alimentar, incluindo frutas, legumes e grãos foi associado a um risco reduzido de fratura em homens e mulheres (LANGSELMO e cols, 2011). Do mesmo modo, TUCKER e cols. (2002) investigaram padrões alimentares entre homens e mulheres com idades 60-93 anos e descobriram que um padrão de dieta rica em frutas, legumes e cereais está associado à maior DMO, enquanto que um padrão alimentar rico em produtos de confeitaria associou-se a menor DMO. MC NAUGHTON e cols. (2011) ao avaliarem 527 mulheres australianas entre 18 a 65 anos identificaram uma associação benéfica à DMO do padrão alimentar que consistia de legumes, sementes, mariscos, frutos secos, vinho, arroz e vegetais.

OKUBO e cols. (2006) ao avaliarem 291 japonesas rurais na pré menopausa demosntraram que o padrão saudável com alto consumo de peixe, frutas, vegetais e baixo consumo de carnes processadas tem efeito benéfico na DMO. Entre as

mulheres gregas, KONTOGIANNI e cols., (2009) descobriram que um padrão alimentar caracterizado por peixe, óleo de oliva, e de baixo consumo de carne vermelha foi associada com maior DMO. Já, mulheres escocesas com idade entre 50 e 59 anos com um padrão alimentar saudável, rico em frutas e vegetais pode levar à menor reabsorção óssea, enquanto que um padrão alimentar rico em alimentos processados está associado a menor DMO (HARDCASTLE e cols. 2011).

Como observado nos diferentes estudos, o padrão alimentar varia segundo a população estudada, mesmo considerando esta variação parece que um padrão alimentar saudável apresenta impacto positivo na DMO.

2.6 DOENÇAS

Alguns estudos revelam associação entre o câncer de mama, endométrio e EDMO (CAULEY e cols., 1996; DOUCHI e cols., 1999; VAN DER KLIFT e cols., 2003; GANRY e cols., 2004; CHEN e cols., 2008).

GANRY e cols. (2004) ao avaliarem 1504 mulheres acima de 75 anos e dividi-las em tercis segundo DMO, evidenciaram que mulheres com DMO superior (DMO do trocanter > 0,704g/cm^2 e DMO do colo do fêmur >0,769g/cm^2) apresentam 2,2 a 2,3 vezes maior risco de câncer de mama quando comparadas à mulheres com DMO inferior. GREINER e cols. (2011) encontraram resultados semelhantes em estudo de coorte, envolvendo 37860 mulheres acima de 50 anos, com divisão em quartis segundo DMO, as mulheres no quartil superior, segundo DMO de coluna lombar, apresentaram 1,32 vezes maior risco de câncer de mama. Os principais mecanismos envolvidos são a associação com maiores concentrações séricas (ETTINGER e cols., 1998) e o polimorfismo do estrogênio (HARVEY, 2005).

Além da condição hiperestrogênica, ressaltam-se a relação com a obesidade tanto pela força mecânica, exercida pelo peso em si, como pela liberação de hormônios provenientes do tecido adiposo (BORBA, 2003; REID e cols., 2006; REID, 2008).

Outro fator implicado parece ser o aumento da conversão do estrógeno no tecido adiposo, gerando consequentemente, uma exposição cumulativa de estrógeno

que contribuiria para EDMO em mulheres obesas e com câncer (DOUCHI e cols., 1999). Adicionalmente, baixas concentrações de globulina ligadora dos hormônios sexuais (SHBG) estão associadas à alta massa gorda (KIRSCHNER e cols., 1990) e a redução destas concentrações pode levar a um aumento dos esteróides sexuais circulantes, podendo contribuir para a EDMO (DOUCHI e cols., 1999; RICCI, 2001).

A hiperinsulinemia também pode ser responsável pelo efeito positivo na DMO, tanto na obesidade, presente ou não em mulheres com câncer, quanto no diabetes. YAMAGUCHI e cols. (2009) demonstram que a hiperinsulinemia pode aumentar a DMO do fêmur em diabéticos do tipo 2. MA e cols. (2012) corroboram para estes resultados, uma vez que indivíduos com diabetes tipo 2 apresentaram 25% a 50% maior DMO quando comparados aos indivíduos controles, não diabéticos. O provável mecanismo se dá em virtude do declínio na produção da proteína 1 de ligação ao fator de crescimento semelhante à insulina (IGFBP-1) e com isso aumentaria a ação do fator de crescimento semelhante a insulina (IGF-1), o qual estimularia a proliferação dos osteoblastos (ALBALA e cols., 1996).

2.7 MEDICAMENTOS

Os medicamentos associados ao aumento da DMO são os diuréticos tiazídicos e as estatinas.

Os diuréticos tiazídicos reduzem a pressão arterial e previnem complicações cardiovasculares decorrentes da hipertensão, além disso, são utilizados no tratamento da nefrolitíase por reduzirem a excreção de cálcio urinário (LaCROIX e cols., 1990).

OLMOS e cols. (2010) ao avaliarem 636 mulheres hipertensas e 343 mulheres saudáveis na pós-menopausa encontraram maior DMO e menor remodelamento ósseo naquelas que faziam uso de tiazídico quando comparadas ao grupo controle. Estudos clínico randomizados mostram um modesto aumento da DMO (LaCROIX e cols., 2000; REID e cols., 2000; BOLLAND, 2007), porém este efeito parece ser dose dependente, sendo mais evidente entre os seis e os doze meses iniciais ao tratamento.

Os mecanismos pelo qual isto ocorre não estão totalmente elucidados. Os tiazídicos reduzem a excreção urinária de cálcio podendo levar a um aumento das concentrações de cálcio sérico, ocasionando redução das concentrações de PTH e diminuição do romodelamento ósseo, porém OTT e cols. (2008) e BOLLAND e cols. (2007) não encontraram alterações nas concentrações séricas de cálcio e PTH.

Outro fator relevante é o aumento do bicarbonato ocasionado pelo tiazídico que altera a excreção urinária de cálcio e a alcalose suave é benéfica aos ossos (LEMANN e cols., 2003).

Adicionalmente, DVORAK e cols. (2007) demonstraram que os tiazídicos podem atuar de forma direta estimulando a formação dos osteoblastos, independente de seus efeitos nos rins, e parece inibir os osteoclastos (HALL e SCHAUEBLIN, 1994) favorecendo a redução da remodelação óssea.

As estatinas são medicamentos utilizados para reduzir as concentrações de colesterol sanguíneo (BUCHER e cols., 1999).

Os resultados dos estudos em relação a sua ação na DMO são conflitantes (RIZZO e cols., 2004).

Estudos observacionais em ratos não levam a resultados conclusivos. Aparentemente a DMO não é alterada (MARITZ e cols., 2001) ou quando ocorre alteração é um modesto aumento na administração crônica (KAWANE e cols., 2004).

Já, em humanos, TANRIVERDI e cols. (2005) ao avaliarem mulheres na pós-menopausa com osteopenia e/ou osteoporose revelaram que o efeito da estatina associada ao uso de bisfosfonato apresenta efeito potencializado quando comparado ao uso do bisfosfonato isolado. As mulheres com o uso de ambas as medicações apresentaram aumento significante na DMO da coluna lombar quando comparadas às mulheres que faziam uso apenas do bisfosfonato. Resultados positivos também foram encontrados por CHUENGSAMARN e cols. (2010) em estudo prospectivo, randomizado, controlado, ao avaliarem 212 pacientes dislipidêmicos com osteopenia, encontraram valores maiores do marcador de formação óssea (P1NP) e valores menores do marcador de reabsorção óssea (CTX) no grupo que recebeu estatina.

Em relação aos marcadores bioquímicos outros estudos demonstram que parece haver um pequeno aumento da osteocalcina (CHAN e cols., 2001) e redução da fosfatase alcalina, podendo ser dose dependente (STEIN e cols., 2001).

Apesar disto, em estudo de revisão de RIZZO e RINI (2006) mostraram que alguns estudos observacionais e prospectivos apresentam resultados conflitantes.

Vale salientar que as estatinas agem na mesma via metabólica dos bifosfonatos, alendronato e residronato, os quais sabidamente reduzem a perda de massa óssea em mulheres com osteoporose pela apoptose dos osteoclatos (GARRET e cols., 2001). Este fato pode contribuir para justificar os efeitos positivos encontrados em alguns estudos.

2.8 PERFIL HORMONAL

Alterações no perfil hormonal refletem na DMO (DELUCA, 2004; HOLICK, 2004b, PERRIEN, 2006; REID, 2008; ARABI e cols. 2012). Os hormônios relacionados à obesidade como a leptina e os hormônios pancreáticos, já foram discutidos anteriormente em antropometria e composição corporal. A seguir serão descritos outros hormônios que interferem na DMO.

2.8.1 Vitamina D e Paratormônio

Em relação ao metabolismo ósseo, sua forma ativa (calcitriol) atua em conjunto com o paratormônio na reabsorção renal de cálcio e na reabsorção óssea. Também aumenta a eficácia da absorção intestinal de cálcio dietético a fim de manter os níveis de cálcio sanguíneos fisiologicamente estáveis (DELUCA, 2004; HOLICK , 2004b).

O consumo de vitamina D e a exposição solar adequada são necessários para a manutenção da $25(OH)D_3$. Em relação ao consumo, poucos são os alimentos que contêm vitamina D e no Brasil, diferente do que ocorre em outros países, não há a fortificação alimentar. Fatores ambientais (latitude, estações do ano, a camada de

ozônio e a nebulosidade) e pessoais (tipo de pele, idade, vestimentas e uso de protetor solar) estão envolvidos com o nível de suficiência ou insuficiência da vitamina D e a saúde óssea (WEBB e cols., 2006; BANDEIRA e cols., 2010; MALLAH e cols., 2011).

Sua deficiência causa osteomalácia e que pode estar acompanhada de baixa massa óssea (DELUCA, 2004; HOLICK, 2004b; HOLICK e cols., 2011).

Estudo realizado por KUCHUK e cols. (2009) em 29 países dos seis continentes em mulheres na pós-menopausa revelam alta prevalência de baixas concentrações séricas da 25(OH)D. Esta deficiência de vitamina D está presente independe da faixa etária e da classe sócio-econômica (SARAIVA e col, 2007; VIETH e col, 2007).

No Brasil, estudo realizado por SARAIVA e cols. (2007) em idosos, revela que 71,2% dos idosos institucionalizados e 43,8% dos idosos não institucionalizados apresentavam concentrações de vitamina D abaixo do mínimo recomendado, segundo os pontos de corte de 20ng/mL. Corroborando com estes resultados GENARO e cols. (2006) encontraram 80% de deficiência de Vitamina D em mulheres na pós menopausa.

A maioria das pesquisas concorda que o melhor indicador para avaliar a adequação de vitamina D é utilizar a 25(OH)D pois além de refletir os estoques obtidos pela absorção da dieta e síntese cutânea, apresenta uma variedade de ensaios clínicos que podem ser utilizados, e adicionalmente se correlaciona com muitas doenças (TRANG e cols., 1998; SAENGER e cols., 2006; HOLICK e cols., 2011).

Estudo realizado em mulheres na pós-menopausa em seis continentes revela que o aumento da 25(OH)D por categoria (<25, 25–50, 50–75, e >75 nM) apresentou declínio significativo de PTH, osteocalcina e CTX, enquanto que a DMO dos sítios avaliados apresentaram um aumento significativo (KUCHUK e cols., 2009), porém não mencionaram EDMO.

Apesar do consenso acerca de qual forma de vitamina D deve-se avaliar, não há um consenso internacional sobre os valores de corte para se definir o estado da vitamina D. Apesar disso, vários autores concordam no valor de 75nmol/L de 25(OH)D,(VIETH, 2004; BOULLON, 2005; GRANT e HOLICK, 2005) com base

no limiar necessário para a supressão máxima do PTH, melhor absorção de cálcio e maior DMO e prevenção de fraturas (DAWSON-HUGHES e cols., 2005).

Em relação ao PTH embora a elevação persistente deste ocasione perda óssea acelerada, a administração intermitente de PTH 1-34 (teriparatida) aumenta a densidade e a qualidade óssea, reduz a taxa de fraturas vertebrais por osteoporose (DATTA, 2011; HAN e cols., 2012; WALSH e cols., 2012), sendo utilizado na prática clínica.

2.8.2 Hormônios sexuais

O hormônio liberador de gonadotrofina (GnRH) é secretado pelo hipotálamo e estimula a secreção do hormônio folículo estimulante (FSH) e do hormônio luteinizante (LH) na adeno-hipófise. Nas mulheres, estes hormônios atuam nos ovários estimulando-os a secretar estrógeno, progesterona e inibina (PRIOR, 2006; SENDAK e cols., 2007). Depois disto, o estrógeno e a inibina, que, por sua vez, regulam a secreção do GnRH, FSH e LH, por mecanismo de retroalimentação (XU e cols., 2009).

A perda desse mecanismo, como na menopausa (hipoestrogenismo), por exemplo, aumenta as concentrações plasmáticas do FSH e LH, que desempenham papel negativo sobre o tecido ósseo (MANSELL e cols., 2007).

Ao contrário do estrógeno e da inibina, que em altas concentrações conferem proteção à massa óssea (PERRIEN e cols., 2006), os hormônios FSH e LH em concentrações elevadas, parecem contribuir para o aumento da reabsorção óssea, porém os resultados são conflitantes.

Alguns estudos demonstram que o aumento sérico de FSH e redução de inibina ocasiona perda óssea em mulheres na perimenopausa (VURAL e cols., 2005; PERRIEN e cols., 2006). Em contrapartida, a redução nas concentrações plasmáticas do FSH parece estar correlacionada com ganho de massa óssea (SOWERS e cols., 2003),

XU e cols. (2009) ao avaliarem 699 mulheres chinesas saudáveis com idade entre 20 e 82 anos, sendo 464 na pré-menopausa e 235 na pós-menopausa demonstraram que os hormônios FSH e LH apresentaram-se aumentados nas mulheres com 40 anos e reduzidos nas mulheres com 60 anos. Em relação à massa

óssea, após divisão em quartis, evidenciaram que a cada aumento de 10 UI/L de FSH e LH resultaram em diminuição de 5,5% e 4,4% da DMO de coluna, respectivamente. Os outros sítios esqueléticos avaliados também apresentaram reduções que variaram entre 2,4% a 4,8%.

Especula-se que o FSH regule diretamente a massa óssea pela estimulação de células de reabsorção óssea (osteoclastos). Estudos *in vitro* evidenciam receptores de FSH na superfície dos osteoclastos (BOYLE e cols., 2003).

Adicionalmente, o FSH estimularia as células imunes a produzir o fator de necrose tumoral alfa (TNF-α) e este, por sua vez, estimularia as células precursoras dos osteoclastos e a diferenciação dos mesmos (IQBAL, 2006; SUN e cols., 2006).

Contrariando os achados descritos anteriormente DRAKE e cols. (2010) realizaram uma intervenção direta na supressão da secreção de FSH, utilizando um antagonista do mesmo, em estudo randomizado, duplo-cego, placebo controlado, envolvendo 46 mulheres na pós-menopausa e não identificaram o FSH como regulador da reabsorção óssea. Indo ao encontro deste achado RITTER e cols. (2008) administraram FSH em ratos machos durante um mês e não verificaram efeito sobre a DMO no fêmur, avaliado por tomografia.

Diante disto o papel do FSH ainda encontra-se incerto, devendo ser investigado. Em relação ao LH e sua influência sobre o tecido ósseo, ainda, não é conhecido, mas especula-se que possa induzir o aumento dos androgênios (BARON, 2006)

2.9 PERFIL LIPÍDICO

Alguns estudos clínicos sugerem a possibilidade de uma relação entre a hipercolesterolemia e massa óssea (KOSHIYAMA e cols., 2001; YAMAGUSHI e cols., 2002; WU e cols., 2003; TANCO e col, 2003; ADAMI e cols., 2004; OROSCO, 2004; CUI e cols., 2005) . Os resultados são controversos, alguns estudos encontraram uma diminuição da DMO (KOSHIYAMA e cols., 2001; YAMAGUSHI e cols., 2002; WU e cols., 2003; TANCO e col, 2003; OROSCO, 2004; CUI e cols., 2005; MAKOVEY e cols., 2009), outros um aumento da DMO (ADAMI e cols., 2004; HERNANDEZ e cols., 2010) e outros ainda não encontraram nenhuma associação (SAMELSON e col, 2004; PLIATSIKA e cols., 2012). Por outro lado,

estudos em modelo animal *in vivo* e *in vitro* encontraram associação entre dislipidemia e massa óssea (PARHAMI e cols., 1999; TINTUT e cols., 2002; TINTUT e cols., 2004).

Os estudos *in vitro* revelaram que produtos da oxidação de lipídeos e lipoproteínas inibem a diferenciação e função osteoblastos (PARHAMI e cols., 1999; TINTUT e cols., 2002).

HERNANDEZ e cols. (2010), em estudo transversal, encontraram baixo *turnover* ósseo, avaliados por Propeptídeo do colágeno tipo1 (P1NP) e Beta-carboxitelopeptídeo (beta-CTX) séricos, em indivíduos hipercolesterolêmicos comparados ao controle. Em contrapartida, estudo caso-controle, realizado por MAJIMA e cols. (2008), ao avaliarem N-telopeptídeo do colágeno (NTx) de pacientes com hipercolesterolemia e compará-lo com controles revelaram aumento no *turnover* ósseo de indivíduos hipercolesterolêmicos, o que sugere a importância da melhora da hipercolesterolemia para não só prevenir a aterogenese, como também a osteoporose.

Os estudos não conseguiram definir, de forma efetiva, a via pela qual isto ocorra, porém parece estar associado à via do mevalonato por estar envolvida na síntese do colesterol, na proliferação de células ósseas e na apoptose de osteoclastos (CUMMINGS e BAUER, 2000; BUHAESCU e cols., 2007).

Diante do exposto torna-se evidente as contradições e dúvidas acerca dos inúmeros fatores que possivelmente determinam a EDMO. No Brasil estudos com estes indivíduos são desconhecidos, reforçando ainda mais a necessidade de aprofundar este assunto.

3. OBJETIVOS

3.1 OBJETIVO GERAL

Identificar os fatores associados à elevada densidade mineral óssea em mulheres adultas.

3.2 OBJETIVOS ESPECÍFICOS

- Artigo 1 – Revisar e discutir os aspectos relacionados à EDMO.

- Artigo 2 – Identificar a prevalência, bem como os fatores de risco e proteção associados com a EDMO em mulheres saudáveis.

- Artigo 3 - Caracterizar o padrão alimentar e pontuar as diferenças existentes no mesmo, de acordo com a DMO.

4. METODOLOGIA

4.1 DELINEAMENTO

Trata-se de um estudo tranversal.

4.2 POPULAÇÃO DO ESTUDO

Foram selecionadas, de forma consecutiva, mulheres que realizaram densitometria óssea (aparelho Lunar-GE) e cujo resultado evidenciou elevada densidade óssea da coluna lombar [maior do que 1,400 g/ cm^2 (T-score maior ou igual a 2,0 desvios-padrão)] e/ ou fêmur proximal [maior do que 1,200 g/ cm^2 (T-score maior ou igual a 2,0 desvios-padrão)], desde que nenhum desses sítios apresentasse osteopenia ou osteoporose. O T-score acima de 2 desvios-padrão foi escolhido após revisão da literatura, que configura esse valor ao diagnóstico de valores acima da normalidade.

O grupo controle foi constituído por mulheres saudáveis, pareadas para a idade e peso, com massa óssea normal (T-score entre + 1 e – 1 desvio-padrão na coluna lombar e no fêmur proximal). O T-score entre 1 desvio-padrão foi escolhido baseado na distribuição da massa óssea, de acordo com a curva de Gauss, ou seja, que utiliza 1 desvio-padrão para identificar 67% da população como normal.

Os dois grupos foram selecionados do banco de dados da *Fundação Instituto de Diagnóstico por Imagem* (FIDI).

De um total de aproximadamente 21.000 densitometrias realizadas na área metropolitana da cidade de São Paulo, foram encontradas 421 com EDMO, destas 381 foram excluídas por não se adequarem ao critério de inclusão (98%) ou não ter interesse em participar do estudo (2%), restando 40 mulheres saudáveis com EDMO, sendo pareadas ao grupo controle em relação à idade e peso.

4.2.1 Cálculo do tamanho amostral

Para o cálculo do tamanho amostral foi utilizada a estimativa de prevalência de elevada DMO em uma amostra de 18.000 densitometrias realizadas. A partir desta estimativa os valores de prevalência foram de 1,31%.

Considerando a prevalência de elevada DMO de 1,31%, o cálculo do tamanho amostral foi realizado segundo LEVINE (2000) e é dado por:

$$n = \frac{(Z\alpha/_2)^2 . p.q}{E^2}$$

Em que:

n= Número de indivíduos da amostra

$Z\alpha/_{2=}$ Valor crítico que corresponde ao grau de confiança desejado 95%

p= Proporção populacional de indivíduos que pertencem à categoria que estudamos

q = Proporção populacional de indivíduos que não pertencem à categoria que estudamos (q=1-p)

E = Margem de erro ou erro máximo de estimativa. Identifica a diferença máxima entre a proporção amostral e a verdadeira proporção populacional (0,05).

O valor obtido foi de 14 mulheres.

4.2.2 Critérios de inclusão

Os indivíduos foram selecionados de acordo com os seguintes critérios:

- Sexo feminino.
- Índice de massa corpórea (IMC) menor ou igual a 29,9kg/m^2.
- Idade entre 30 e 65 anos, ou seja, após o pico de massa óssea e antes da senescência, a fim de afastar problemas degenerativos da coluna lombar, que pudessem superestimar a real densidade óssea vertebral.
- Etnia branca, caucasóide, parda ou oriental.

4.2.2. Critérios de exclusão

- Sexo masculino.
- IMC maior do que 29,9 kg/ m^2 e menor do que 18,5 kg/ $m,^2$ baseado na classificação da OMS (2000).

- Etnia negra
- Indivíduos com histórico de etilismo.
- Indivíduos dislipidêmicos.
- Indivíduos portadores de hepatite C.
- Presença de alterações degenerativas em coluna lombar evidenciadas com radiografia simples da coluna lombar.
- Indivíduos com alguma deficiência cognitiva que os impossibilitem de fornecer respostas adequadas, tais como seqüelas neurológicas ou demências senis.
- Uso de medicações que interferem no metabolismo ósseo, inclusive tiazídicos e estatinas.
- Doenças associadas com desequilíbrio nutricional e metabolismo óssea, como doença renal, infecciosas, digestivas, neoplásicas, endócrinas, doenças reumáticas e doenças cardiovasculares, sendo obtidas por auto-relato.

Os indivíduos foram informados sobre o estudo e, concordando em participar, assinaram um termo de consentimento (Anexo I) para responderem aos questionários e realizarem os exames bioquímicos e radiológicos previstos. Caso o tempo de realização do DXA fosse superior a seis meses o indivíduo era informado que o exame seria realizado novamente.

4.3 PROTOCOLO DE ESTUDO

As mulheres foram avaliadas após explicação do projeto e assinatura do termo de consentimento (Anexo I), conforme preconiza a resolução n° 916 do Conselho Nacional de Saúde, de 10 de Outubro de 1996.

O estudo constou de avaliações antropométrica, radiológica, de densidade mineral óssea, composição corporal e do perfil bioquímico. Além disso, foram aplicados três questionários validados a fim de avaliar fatores de risco da massa óssea (Anexo II), fatores nutricionais (Anexo III) e escore de atividade física (Anexo IV), com a finalidade de identificar todos os possíveis fatores associados à EDMO.

4.3.1 Etnia

Diante da grande miscigenação que ocorre no Brasil optou-se por classificar em brancos e não brancos. Vale salientar que as mulheres negras foram excluídas do estudo.

4.3.2 Avaliação antropométrica

A avaliação antropométrica foi realizada por meio da aferição do peso e estatura de acordo com as técnicas propostas por FRISANCHO (1993):

Peso: medido em quilograma (kg). As pacientes utilizaram roupas leves e estavam descalças, sendo posicionadas sobre a balança do tipo plataforma , marca Filizola®, com capacidade para 150 kg e precisão de 100g.

Estatura: foi utilizado o estadiômetro da própria balança. As pacientes foram orientadas a permanecer de costas para o estadiômetro, em posição ereta e com os pés unidos. O plano horizontal de Frankfurt foi utilizado nesta aferição (parte inferior do globo ocular em linha horizontal com o conduto auditivo externo). A leitura foi realizada no centímetro mais próximo, com variação de 0,5 cm, quando a haste do estadiômetro recostava sobre a cabeça.

Com estes dados foi calculado o IMC (Índice de Massa Corporal), definido como massa corporal em quilos dividido pela estatura em metros quadrados (kg/m^2), sendo classificados de acordo com os critérios propostos pela Organização Mundial da Saúde (OMS, 2000).

Quadro 1: Classificação do Índice de Massa Corporal (IMC)

IMC (Kg/m²)	*Classificação*
<16	Magreza grau III
16,0 – 16,9	Magreza grau II
17,0 – 18,4	Magreza grau I
18,5 – 24,9	Eutrófico
25 – 29,9	Pré-obeso
30 – 34,9	Obesidade grau I
35 – 39,9	Obeisidade grau II
≥40	Obesidade grau III

Fonte: OMS, 2000

4.3.3 Avaliação radiológica:

A avaliação radiológica da coluna lombar (L1 a L4), nas posições póstero-anterior e perfil, foi realizada por um reumatologista para excluir processo degenerativo vertebral ou outras causas de elevada massa óssea, tais como metástases ósseas, doença de Paget, fratura ou deformidades congênitas (hérnia de Schmorl, escoliose grave). Os seguintes critérios foram utilizados no protocolo de aquisição das imagens pela radiologia convencional da coluna vertebral: distância do tubo-filme foi de 120 cm, com feixe de raios X centrado em L3.

4.3.4 Avaliação da Densidade Mineral Óssea :

O estudo da densidade mineral óssea foi realizado na coluna lombar e fêmur proximal, utilizando-se o densitômetro de dupla emissão com fonte de raios X (*GE Lunar Radiation Corporation*, modelo DPX, Madison, WI, USA). Esse exame foi realizado previamente, uma vez que constitui critério de inclusão.

O procedimento técnico padrão foi adotado para o posicionamento dos pacientes para a realização do exame com controle de qualidade diário. Assumimos os dados de referência do fabricante (NHANES), que são semelhantes à curva normal brasileira. O modo médio (*medium scan mode*) e a análise é feita com o

programa Lunar versão 3,6 z. Tanto a aquisição do exame quanto a análise da densidade mineral óssea foram realizadas pelo mesmo examinador na mesma visita. O coeficiente de variação do método em nosso serviço é de 3,6% para o fêmur e de 2% para a coluna. Controle de qualidade do aparelho foi realizado diariamente, conforme instruções do fabricante.

As pacientes que foram recrutadas e haviam realizado a avaliação da DMO em período superior a seis meses a avaliação foi realizada novamente no Hospital São Paulo, caso contrário o exame realizado anteriormente era utilizado.

4.3.5 Avaliação da composição corporal

Para avaliação da composição corporal foi empregada a densitometria de corpo total, pelo densitômetro de dupla emissão com fonte de raio-X (*GE Lunar Radiation Corporation, modelo DPX IQ, Madison, WI, USA, versão 4.7e*), sendo avaliados massa magra e gordura corporal total. O local de realização do exame foi o Hospital São Paulo. As pacientes permaneceram deitadas, os braços paralelos ao corpo e com as pernas afastadas durante a execução do exame.

A obtenção da composição corporal neste método é feita pela medida de atenuação dos picos fotoeletrólitos no corpo. A estimativa do conteúdo de gordura em massa magra sem tecido ósseo é derivada a partir de uma constante de atenuação de gordura pura e de massa magra sem osso. Ao final do exame é possível quantificar a massa magra sem tecido ósseo, massa gorda e partes moles sem gordura (COSTA, 2001).

Foram avaliados valores de Massa Magra Total (MMT), valor em gramas, Massa Muscular Esquelética Total (MMET), valor em quilos, sendo a soma da massa magra das pernas e dos braços. O Índice de Massa Muscular Esquelética (IMME), que relaciona a massa magra das pernas e dos braços em quilos do indivíduo dividido pelo quadrado da estatura em metros foi calculado (BAUMGARTNER e cols., 1998), ou seja:

$$\text{IMME} = \text{Braços} + \text{Pernas (massa magra kg)} / \text{Altura}^2 \text{ (cm)}$$

Em relação à gordura corporal total é avaliada em kg e na forma de porcentagem de gordura corporal (%GC).

4.3.6 Parâmetros bioquímicos

Após jejum de doze horas foram coletados 20 ml de sangue de todas as participantes do estudo para a análise dos parâmetros bioquímicos, bem como a urina de 24 horas.

As análises laboratorias foram realizadas, em sua maior parte, pelo Laboratório Central do Hospital São Paulo. As dosagens de vitamina D, IGF-1, PTH intacto, CTX sérico, FSH, LH e leptina foram realizadas pelo Laboratório Cura Imagem e Diagnóstico.

Marcadores bioquímicos do metabolismo ósseo:

- Dosagem sérica de cálcio total: método colorimetrico
- Dosagem sérica de cálcio iônico: método eletrodo íon seletivo.
- Magnésio: método colorimétrico.
- Fósforo: método fosfomolibdato UV.
- Fosfatase alcalina: método cimético enzimático/ eletroforese em gel de agarose.
- Calciúria 24h: método colorimétrico.
- Fosfatúria de 24h: método fosfomolibdato UV.
- *Clearance* de Creatinina: método cinético colorimétrico.
- Sódio urina 24h: método potenciométrico.
- Vitamina D (25OHD): método radioimunoensaio.
- IGF-1: método imunofluorométrico.
- PTH intacto: método imunoradiométrico.
- CTx sérico: método eletroquimioluminométrico.

Avaliação Metabólica Global:

- Glicemia de jejum: método enzimático calorimétrico.
- Ácido úrico: método enzimático calorimétrico.
- Colesterol total e frações: método Trinder.
- Triglicérides: método Trinder.

Avaliação do Perfil Hormonal:

- Dosagem sérica de leptina: método radioimunoensaio.

- Dosagem sérica de estradiol: método eletroquimioluminométrico.
- Dosagem sérica de testosterona livre e total: método radioimunoensaio.
- Dosagem sérica de prolactina: método fluorimetrico.
- Dosagem sérica de FSH: método fluorimetrico.
- Dosagem sérica de LH: método fluorimetrico.

Avaliação do Perfil Infeccioso:

- Sorologia para vírus B: método eletroquimioluminométrico.
- Sorologia para vírus C: método eletroquimioluminométrico.

4.3.7 Avaliação dos fatores relacionados à massa óssea

A investigação de fatores relacionados à massa óssea foi baseado no modelo de questionário utilizado no Ambulatório de Reumatologia (ANEXO II).

4.3.8 Avaliação do Consumo Alimentar

Para a avaliação da dieta habitual das pacientes foi aplicado o Questionário de Freqüência Alimentar (QFA) quantitativo (Anexo III), considerando período de seis meses, juntamente com um álbum fotográfico para facilitar a visualização do tamanho das porções.

Optou-se pelo QFA devido a sua habilidade em estimar durante um período considerável de tempo a ingestão habitual, possuir um baixo custo e por ser bastante utilizado neste tipo de estudo.

O questionário utilizado é composto por 62 itens alimentares e foi validado para avaliação da ingestão alimentar de mulheres com osteoporose (PEREIRA e cols., 2008).

Para cada alimento do QFA as participantes informam a freqüência média usual de consumo nos últimos 6 meses, a respectiva unidade de tempo (diariamente, semanalmente, quinzenalmente, mensalmente, a cada 2 meses ou nunca) e qual o tamanho de sua porção individual usual (pequena, média, grande ou extragrande), auxiliada pelo álbum fotográfico.

Os dados obtidos no QFA foram codificados e digitados duplamente, sendo convertidos em energia e nutrientes (proteína, carboidrato, lipídio, cálcio, fósforo e vitamina D),com o auxílio do software *Dietsys (Dietary Analisys System)*, versão 4.0 desenvolvido pelo instituto do câncer dos EUA. Os nutrientes analisados foram incorporados ao software, sendo todos oriundos do United States Department of Agriculture (USDA).

São utilizados os valores propostos pelo Institute of Medicine – DRI's (1997-2003, 2011), para a avaliação da adequação da dieta, que estabelece as necessidades de acordo com gênero e estágios de vida para a população saudável.

A correção pela energia foi feita computando-se os resíduos de modelos de regressão, com a ingestão energética como variável independente e a ingestão dos nutrientes como variável dependente, segundo o método proposto por Willet e Stampfer (1986).

Para a avaliação do padrão alimentar os alimentos foram sistematicamente agrupados com base em semelhanças de alimentos e composição de nutrientes, reduzindo assim os 62 alimentos a 10 grupos de alimentos. Os seguintes grupos de alimentos foram formados: alimentos ricos em gordura (manteiga, margarina, óleo de oliva, óleo de soja, maionese e salada de maionese); bebidas alcoólicas (fermentadas e destiladas); bebidas não alcoólicas (café, chá e refrigerante); carnes e ovos (carne bovina, suína, aves, peixes, ovo de codorna, frango, ovo e omelete); carnes processadas (salame, salsicha e presunto); cereais e tubérculos (arroz, batata, pão, bolachas, macarrão, farinha de mandioca e farofa); doces (sobremesas, biscoitos recheados, chocolate doce gelado e açúcar), frutas e legumes (uva, banana, laranja, tangerina, mamão, maçã, pêra, melancia, melão, manga, abacaxi, goiaba, caqui, suco de frutas natural, alface, acelga, tomate, couve, espinafre, beterraba, cenoura, pepino, pimentão, berinjela, brócolis, couve-flor e legumes de sopa); feijão (feijões, ervilhas, lentilhas e soja), produtos lácteos (leite, iogurte e queijo).

Na aplicação do QFA é questionado o uso de suplementação pelas entrevistadas, sendo este dado posteriormente computado.

4.3.9 Avaliação da Atividade Física

Para a avaliação da atividade física habitual, foi utilizado o questionário proposto por BAECKE e cols. (1982), validado para o português por FLORINDO (2004), com isso avaliou-se quatro níveis de atividade física, sendo: atividade física ocupacional (questões 1 a 8), exercício físico e atividade física de lazer (questões 13 a 16) e atividade física de locomoção (questões 13 a 16), as quais compõem a avaliação da atividade física habitual (Anexo IV).

Para a classificação da atividade física habitual, foi utilizada a fórmula proposta por BAECKE e cols. (1982), resultando em 9 escores finais. Para a classificação dos níveis de gasto energético das atividades físicas ocupacionais e das modalidades de exercícios físicos que não constavam da padronização de BAECKE e cols. (1982) foi utilizado como referência o estudo de AINSORTH e cols. (2000) que discorre sobre compêndio de classificação de gasto energético de atividades humanas.

Cálculo do questionário:

Atividade Física Ocupacional (AFO)

Escore de AFO = (questão 1 + questão 2 + questão 3 + questão 4 +questão 5 +questão 6 + questão 7 + questão 8) / 8

Cálculo da primeira questão referente ao tipo de ocupação:

Intensidade (tipo de ocupação) = 1 para profissões com gasto energético leve ou 3 para profissões com gasto energético moderado ou 5 para profissões com gasto energético vigoroso.

Exercício Físico no Lazer (EFL)

Cálculo da questão 9 referente a prática de esporte/exercício físico:

Intensidade (tipo de modalidade) = 0,76 para modalidades com gasto energético leve ou 1,26 para modalidades com gasto energético moderado ou 1,76 para modalidades com gasto energético vigoroso.

Tempo (horas por semana) = 0,5 para menos de uma hora por semana ou 1,5 entre maior que uma hora e menor que duas horas por semana ou 2,5 para maior que duas horas e menor que três horas por semana ou 3,5 para maior que três e até quatro horas por semana ou 4,5 para maior que quatro horas por semana (determinado pela resposta das horas por semana de prática).

Proporção (meses por ano) = 0,04 para menor que um mês, ou 0,17 entre um e três meses ou 0,42 entre quatro e seis meses ou 0,67 entre sete e nove meses ou 0,92 para maior que nove meses (determinado pela resposta dos meses por ano de prática).

Para o cálculo desta questão, os valores são multiplicados e somados: Modalidade 1 = (intensidade x tempo x proporção) + Modalidade 2 = (intensidade x tempo x proporção).

Após o resultado deste cálculo, para o valor final da questão 9, foi estipulado um escore de 1 a 5 de acordo com os critérios especificados no Quadro 3.

Quadro 2: Critérios propostos para a classificação da prática de esporte/exercício físico de lazer em escores

Valor encontrado	Escore Correspondente
0 (sem exercício físico)	1
Entre 0,001 até <4	2
Entre 4 até < 8	3
Entre 8 até < 12	4
≥12	5

Fonte: Baecke e cols., 1982

Os escores das questões 10 a 12 foram obtidos de acordo com as respostas das escalas de Likert. O escore final de EFL foi obtido de acordo com a fórmula especificada abaixo:

Escore de EFL = questão 9 + questão 10 + questão 11 + questão 12 / 4

Atividade Física de lazer e Locomoção (ALL)

Os escores das questões 13 a 16 foram obtidos de acordo com as respostas das escalas de Likert. O escore final de ALL foi obtido de acordo com a fórmula especificada abaixo:

Escore de ALL =(6 – questão 13) + questão 14 + questão 15 + questão 16/ 4

4.4 ANÁLISE ESTATÍSITCA

A análise descritiva dos dados foi realizada inicialmente com o intuito de conhecer as características gerais da população: média e desvios-padrão.

A distribuição normal foi verificada por meio do teste Kolmogorov-Smirnov. Para as variáveis com distribuição normal foi aplicado o teste *t-student* para comparação de médias (duas), enquanto as variáveis categóricas foram analisadas pelo teste de associação do qui-quadrado. A correlação entre as variáveis foram avaliadas por testes paramétricos e correlação de *Pearson*.

Os modelos de regressão linear múltipla foram utilizados a fim de identificar fatores associados com a EDMO, utilizada como variável dependente. As características gerais e clínicas, dados de consumo alimentar, escore de atividade física, medidas da composição corporal, concentrações dos parâmetros bioquímicos foram consideradas como independentes. Valor de $p<0,05$ foi considerado como significante.

A análise fatorial exploratória dos dez grupos de alimentos foi utilizada para a avaliação dos padrões alientares. Os dados foram verificados usando o Kaiser-Meyer-Olkin (KMO) de medição da adequabilidade da amostra e o teste de esfericidade de Barlett (BTS), o qual testa a presença de correlações entre as variáveis.

Todas as análises foram realizadas com o auxílio do *Statistical Package for the Social Sciences*, versão 16.5 para Windows (SPSS Inc, Chicago, IL).

4.5 ASPECTOS ÉTICOS

Este trabalho foi aprovado pelo Comitê de Ética em Pesquisa (COEP) da Faculdade de Saúde Pública da Universidade de São Paulo de acordo com as diretrizes e normas que regulamentam as pesquisas envolvendo seres humanos, aprovada pela resolução n° 196, de 10 de outubro de 1996, do Conselho Nacional de Saúde. Protocolo de pesquisa n°0170/09 (Anexo V).

5. RESULTADOS

Artigo 1:

"High Bone Mineral Density and Bone Heatlh"

Artigo de revisão

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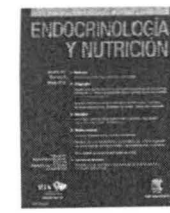

SHORT REVIEW

High bone density and bone health

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KEYWORDS
Bone and bones;
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Abstract The aim of this paper is to review the main aspects related to high bone density (HBD) as well as to discuss the physiologic mechanisms involved in bone health. There are still no well-defined criteria for identification of individuals with HBD and there are few studies on the topic. Most studies demonstrate that overweight, male gender, black ethnic background, physical activity, calcium and fluoride intake and use of medications such as statins and thiazide diuretics play a relevant and positive role on bone mineral density. Moreover, it is known that individuals with certain diseases such as obesity, diabetes, estrogen receptor-positive breast or endometrial cancer have greater bone density than healthy individuals, as well as athletes having higher bone density than non-athletes does not necessarily mean that they have healthy bones. A better understanding of risk and protective factors may help in the management of patients with bone frailty and have applicability in the treatment and in the prevention of osteoporosis, especially intervening on non-modifiable risk factors.

PALABRAS CLAVE
Hueso y huesos;
Dieta;
Densidad ósea

Densidad ósea elevada y salud ósea

Resumen El objetivo de este artículo es revisar los aspectos principales relacionados con la Densidad Ósea Elevada (DOE) y analizar los mecanismos fisiológicos implicados en la salud ósea. No existen aún criterios bien definidos que sirvan para identificar a los individuos con DOE, y los estudios sobre el tema son escasos. La mayoría de los estudios demuestran que el exceso de peso, el sexo masculino, la raza negra, la actividad física, la ingesta de calcio y flúor y el uso de medicamentos como las estatinas y los diuréticos tiazídicos desempeñan un papel relevante y positivo en la Densidad Mineral Ósea (DMO). Además, se ha observado que los individuos con enfermedades tales como obesidad, diabetes, cáncer de mama positivo para receptores de estrógenos o cáncer del endometrio tienen mayor DMO que los individuos sanos; del mismo modo, se observa una mayor DMO en atletas frente a los que no lo son, sin que

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ello necesariamente sea sinónimo de salud ósea. Un mejor entendimiento de los factores de riesgo y de protección podría ayudar a mejorar el tratamiento de los pacientes con fragilidad ósea e incidir en la prevención de la osteoporosis, especialmente en los factores de riesgo no modificables.

Introduction

The high prevalence of osteoporosis and fractures due to bone frailty worldwide underscores the importance of seeking new prevention and treatment strategies,[1] such as the identification of factors involved in the increase of bone mineral density (BMD) for possible applicability in high risk populations. Few studies have addressed the prevalence of high BMD or the main clinical and laboratory aspects of individuals with high BMD. Most of these studies indicate that the following factors seem to have a positive influence on bone density: anthropometric factors (weight and body mass index [BMI] above 30 kg/m^2),[2] demographic factors (male gender, black ethnic background),[3] genetic factors (LRP 5 mutations),[4] healthy lifestyle habits (regular physical activity,[5] calcium intake above 1500 mg/day)[6] and use of medications such as statin[7] and thiazide diuretics.[8] Moreover, individuals with certain diseases as obesity, estrogen receptor-positive breast or endometrial cancer[9,10] and type II diabetes[11] have greater BMD than that of healthy individuals and among healthy subjects as athletes have greater bone density than non athletes.[12] Based on the items addressed in the studies cited above, the aim of this paper is to review and discuss the aspects related to high BMD and to bone health.

High bone mineral density

The occurrence of high bone density (HBD) has been described in the literature in the last ten years. However, yet there are no well-defined criteria for adequate and precise identification of HBD. In 1994, the World Health Organization defined criteria to characterize normal and low bone density (osteopenia and osteoporosis).[13] However, there is currently no consensus on the cutoff point for the definition of individuals with high BMD.

A cohort study involving more than 1800 women[14] suggests that the cutoff point for high BMD is 1.209 g/cm^2 for the femoral neck and 1.228 g/cm^2 for the lumbar spine (upper quartiles). Assessing more than ninety six thousand bone densitometry exams, Gregson et al.[15] defined *Z*-score equal to or greater than 3.5 standard deviations for spine and/or hip for the characterization of such individuals; based on this criterion, only 169 individuals with HBD were found (approximately 0.2% of the overall sample). Beginning with the premise that a *T*-score less than or equal to −2 standard deviations indicates low bone density and so a greater risk for fractures, it is reasonable to assume that a *T*-score above +2 standard deviations in the absence of fractures or diseases known to affect bone quality to define HBD.

However, there is no reference in these definitions regarding the relation between high bone mass and bone health reflected by a lower rate of stress or bone frailty fractures and better bone quality and strength. In other words, it is not known if higher BMD is truly associated with bone healthy.

The main factors associated to HBD are unknown.[4] Genetic, mechanical, environmental, nutritional and endocrine factors are among the determinants related to the acquisition peak bone mass, to bone health and potential factors associated with HBD are discussed below.

Genetic factors

Genetic factors account for 75–80% of the variation in bone mass peak.[16] An increase in bone mass may be caused by rare (often hereditary) osteochondrodysplasias and a variety of dietetic, metabolic, endocrine, hematological, infectious and neoplastic disorders.[17]

Low-density lipoprotein receptor-related protein 5 (LRP5) gene mutations and some other mutations are among the most studied genetic factors.

LRP5 is involved in the Wnt canonical signaling pathway, in which it acts as a coreceptor and regulator of the intracellular signaling of β-catenin. Expressed in various tissues, LRP5 is considered a key protein for the physiology of bone tissue as well as in different pathological processes that include bone formation or neoformation.[18] Mutations in the LRP5 gene are responsible for bone abnormalities, such as high bone mineral density and osteoporosis-pseudoglioma syndrom.[4]

Genetic mutations and gene polymorphisms may cause either positive or negative phenotype modifications in bone tissue. Thus, it is of clinical importance to know whether an excess in expression or gain in function of a particular gene, such as VDR, could be associated to high BMD or to a lesser risk of fractures.

Non-genetic factors

Non-genetic factors account for 20–25% of peak bone mass and may change over time. The main modifiable factors and physiopathogenic mechanisms suggested for health and increase in bone mineral density are displayed in Table 1.

Details on the positive influence of these factors on bone tissue are provided below.

Anthropometrics and body composition

The vast majority of studies include body weight as a positive factor for bone density with 10–20% of the variation in bone density related with high BMI.[19] In a cohort study carried out with more the sixteen thousand women over

Table 1 *Modifiable risk and protection factors and physiopathogenic mechanisms proposed to explain the association between high bone density and bone health.*

Associated factors	*Proposed physiopathogenic mechanisms*
Body mass index	• Mechanical force exercised by weight itself
Lean mass	• ↑ mechanical stress
Fat mass	• ↑ leptin → regulates development of osteoclasts, ↓ RANK and RANK-L production, ↑ OPG → inhibition of osteoclastogenesis
	• Hyperinsulinemia + greater quantity of fat tissue → ↑ concentrations of sex hormones → ↓ osteoclast activity → positive effect on osteoblasts
	• ↑ amylin → potentially inhibits bone resorption
	• ↑ preptin → ↑ osteoblast activity
	• ↑ ghrelin → stimulates proliferation and differentiation of osteoblasts, but results in humans remain contradictory
Physical activity	• Muscle contraction → ↑ muscle fibers
	• Impact provided by exercise → adaptive mechanical osteogenic response
	• Release of anabolic hormones → signals for osteogenic response
	• Piezoelectric effect → stimulates cell activity → depositing of minerals in points of interest
Nutritional factors	• Protein → regulates hepatic production and plasma concentration of IGF-1
	• Calcium → maximizes peak bone mass, maintains bone mass in adulthood and minimizes bone loss stemming from ageing
	• Vitamin D → acts on intestinal absorption of calcium and bone mineralization
	• Phosphorus → regulation of plasma concentrations of calcium and PTH
	• Antioxidants:
	- Hydroxylation and formation of collagen
	- Inhibition of transcription factor, which regulates osteoclastogenesis and protects cells from lipid peroxidation
	- Influence osteoblast activity and protect against damage from oxidative stress
Thiazide diuretics	• ↓ excretion of calcium → ↑ plasma concentration of calcium → ↓ PTH → ↓ bone remodeling; positive calcium balance
	• ↑ serum bicarbonate → alteration in urinary excretion of calcium; discreet alkalosis is beneficial to bone tissue
	• Direct action → stimulation of osteoblastogenesis and inhibition of osteoclasts → ↓ bone remodeling
Statins	• Same metabolic pathway as bisphosphonates → osteoclast apoptosis
Vitamin D and parathyroid hormone	• Renal calcium reabsorption; bone resorption; bone mineralization
	• ↑ efficiency of intestinal absorption of dietary calcium → maintenance of physiologically stable serum calcium concentrations

RANK: receptor activator of nuclear factor Kβ; RANK-L: receptor activator of nuclear Kβ ligand; OPG: osteoprotegerin; IGF-1: insulin-like growth factor; PTH: parathyroid hormone.

50 years of age, Morin and Leslie[20] found that the proportion of women with high BMD increased significantly with BMI and that low BMI was associated to a greater risk of low bone density and osteoporotic fractures.[21] With regard to body composition, an increase in lean mass in respect to fat mass leads to an increase in muscle strength and stimulates bone formation (osteoblasts and osteocytes) through mechanical stress.[22] According to most authors, the higher proportion of lean mass is the main determinant of bone density.[22,23] and adipose mass contributes in a less important manner.

Regarding the role of fat tissue on bone cells, it is speculated that one of the main implicated physiopathogenic mechanisms is an increase in serum concentrations of leptin, which is a hormone secreted by adipocytes that directly inhibits osteoclastogenesis *via* the RANK/RANKL/OPG system. Leptin also acts indirectly through the hypothalamus, especially by decreasing in bone formation rate. Moreover, in obese individuals, there is an increase in the secretion of pancreatic hormones (insulin, preptin and amylin), which have a positive effect on bone tissue. Hyperinsulinemia associated to a greater amount of fat tissue results in several abnormalities, such as increased ovarian production of estrogen and reduced hepatic synthesis of sex-hormone binding proteins. Amylin is secreted together with insulin and inhibits bone resorption, while preptin increases osteoblast activity, especially in obese individuals.[10] Ghrelin is mostly synthesized by cells of the gastric fundus and is able to stimulate the proliferation and the differentiation of osteoblasts[25] as well as to activate osteoclastogenesis during periods of fasting *in animal models*. These results are contradictory in humans, where

ghrelin levels are being closely related to BMD in adolescent women, but the same may not occur in older men and women.[10]

Is important to stand out the fat mass contributed in a less important manner than lean mass to bone formation, since it is frequently associated with other metabolic disorders such as diabetes, cardiovascular diseases and some neoplasms.

Ethnic background

African American women have greater bone mass compared with Caucasian women.[24] Greater renal resorption of calcium and resistance to PTH is one of the main mechanisms proposed for this finding.[25] Moreover, the higher lean mass observed in African American, especially related to muscle modulation by traction (biomechanical force), might be associated with lower risk of fractures in both genders.[26]

Physical activity

The benefits of physical activity on bone mass are widely recognized, particularly the effect on muscle contraction (recruitment and activation of muscle fibers)[5] with the impact on bone cells, which favors periosteal apposition (adaptive mechanical response) and release of osteoanabolic hormones, such as growth hormone, insulin-like growth factor (IGF-1), estrogen and PTH.[27] Besides, strain-related adaptation is essential for normal bone development and regulation of strength in relation to exercise.

It is well known that the mechanical loads can stimulate responses from osteocytes and bone lining cells. Osteocytes probably do not respond directly to mechanical strain (deformation) of bone tissue, but respond indirectly to extracellular fluid flow caused by loading. Osteocytes exposed to fluid shear stress release several messengers, including prostaglandins and nitric oxide.[28] Osteoblasts also secrete these substances, as well as they express several growth factors. Mechanical stimuli can also affect osteoclasts, but this effect appears to be indirect. Loading increases hydrostatic pressure within the bone marrow, which may induce a decrease in osteoclast differentiation through marrow stromal cells participation. When exposed to strain, preosteoblastic marrow stromal cells reduce expression of RANK-L, which in turn decreases osteoclast number.[29] Consequently, cells of osteoblastic lineage appear to be mediators of the suppressive effects of mechanical stimuli on bone resorption.[30]

Mechanical stress also improves bone strength by influencing collagen alignment as new bone is being formed. Cortical bone tissue located in regions subject to predominantly tensile stresses has a higher percentage of collagen fibers aligned along the bone's long axis.

In regions of predominant compressive stresses, collagen fibers are more likely to be aligned transverse to the long axis.[31]

These aspects have been demonstrated along with an increase in osteocalcin and N-terminal propeptide of type 1 procollagen (PINP)[32] and greater bone density in high-performance athletes (resistance and impact activities),[12] although with contradictory results depending on the type of training used on women in the pre-menopause and post-menopause periods.[33]

In a review article, Wallace and Cumming[34] demonstrate the positive effects of physical activity (exercises with and without impact - running and weight lifting, respectively) on vertebral bone density. Aquatic activities, however, such as swimming and water aerobics, do not offer consistent benefits to bone health.[35]

The American College Sports of Medicine (ACSM) suggests that an increase in bone density occurs in adults only with high-intensity aerobic and resistance exercises. The frequency varies in accordance with the modality. The ACSM recommends three to five sessions of impact exercises a week and two to three sessions of resistance exercises, with each session lasting 30-60 min.[36]

Nutritional factors

While there is evidence regarding the association between bone mass and inadequacy of micro and macronutrients, there are few studies that relate dietary intake to HBD.

Protein

Protein is a primary component of bone tissue and has an osteoanabolic effect, mainly in individuals with adequate calcium intake. Dietary protein regulates the hepatic production and plasma concentrations of the growth hormone and IGF-1, which are responsible for differentiation, maturation and recruitment of osteoblasts.[37] While diets with protein restriction may reduce bone density,[37] protein-rich diets have shown conflicting results. Hunt et al.[38] found that an increase in IGF-1 following the ingestion of proteins had a beneficial effect on bone metabolism. However, it should be pointed out that increase in protein intake also led to a greater kidney excretion of calcium and could therefore have a negative effect on bone density,[39] which may be minimized when there is adequate calcium and vitamin D intake.[40]

Calcium and vitamin D

Calcium is the most abundant mineral in the organism and nearly 99% is found in the bones and teeth. Calcium is involved in biological functions, such as muscle contraction, mitosis, blood coagulation, mineral reserves and homeostasis, synapses and structural support.[41] In bone tissue, calcium is extremely important for maximizing peak bone mass and maintaining it throughout adult life and for minimizing bone loss during ageing.[42]

Data obtained by dietary survey in regions of the State of São Paulo, Brazil, demonstrated that mean calcium intake was low for age and gender (483 mg/day for women and 410 mg/day for men).[43] This low intake was also demonstrated in the Brazilian Osteoporosis Study (BRAZOS), which describes a mean *per capita* intake of 400 mg/day,[44] with statistically significant differences between regions of the country, genders and age groups. According to Pereira et al.,[45] the main reasons for this low calcium intake are the high cost of the main food sources as well as regional, cultural and dietary habits.

Moreover, the bioavailability of calcium is dependent on exogenous factors, such as phytates, oxalates, tannins and sodium, which play a negative role in absorption, and on endogenous factors, such as age, physiological conditions and hormonal regulation. On the other hand, oligosaccharides may maximize calcium absorption, as these molecules increase intestinal fermentation and the production of short-chain fatty acids able to acidify the medium and to stimulate the calcium absorption.[45] It is also important to highlight the role of vitamin D in increasing absorption of this mineral.[46] However, no study has yet demonstrated the relation between dietary calcium and high BMD.

Phosphorus

Phosphorus is essential for bone formation and highly related to concentrations of calcium and PTH. A high phosphorus intake, together with low calcium intake, may alter mineral and bone metabolism due to increase in the secretion of PTH[47] and greater gene expression of RANK/RANKL with a consequent stimulus of osteoclastogenesis.[48] Pinheiro et al.[44] found that each 100 g of phosphorus ingested increased the risk of fracture by 9%. However, diets with phosphorus restriction do not promote increase of bone mineral density. Indeed, they may cause a negative phosphorus balance, thereby leading to greater bone loss. Thus, adequate intake of phosphorus and calcium is essential to bone mineralization.

Antioxidants

Antioxidants from the diet, such as selenium, vitamin C and vitamin E, are capable of reducing the adverse effects of reactive oxygen species (ROS) on cell physiology.[49]

Formation of ROS is an unavoidable outcome of life in an oxygen-rich environment and occurs primarily in the mitochondria from the escape of electrons passing through the electron transport chain during aerobic metabolism.[50] ROS are also generated during fatty acid oxidation or in response to external stimuli, such as inflammatory cytokines, growth factors, environmental toxins, chemotherapeutics, UV light, or ionizing radiation and is associated with ageing, diabetes, atherosclerosis and osteoporosis.[51]

Several *in vitro* studies and animal models have demonstrated that oxidative stress has an important impact on the differentiation and function of osteoclasts[52,53] as well as the pathogenesis of bone loss.[54]

Osteoporotic women have low plasma concentrations of vitamin E,[53] which together with low intake of this antioxidant may increase the risk of fractures among smokers. In contrast, the high consumption of fruits and vegetables has a positive effect on bone mass,[55] although no studies have demonstrated its association with high BMD.

Diseases

One could assume that higher BMD could be related to greater bone strength and lower fracture risk and, thus, better bone health. However, several diseases are associated with BMD values above normal limits, as some estrogen receptor-dependent cancers and other genetic diseases such as osteopetrosis, osteosclerosis and van Buchem disease. Studies have demonstrated a significant association between high BMD and estrogen receptor-positive breast and endometrial cancer.[9,56] Assessing more than 1500 elderly women. Ganry et al.,[56] found that those with femoral neck bone density above 0.769 g/cm^2 had a two-fold greater risk of breast cancer. The main mechanisms involved are greater serum concentrations and estrogen's gene polymorphism.[57]

There is also an association of HBD with obesity, due to the mechanical strength exercised by weight itself as well as the release of hormones from fat tissue (peripheral conversion of female hormones,[10] low concentrations of sex hormone-binding globulin[58] and hyperinsulinemia or peripheral resistance to insulin[11]). Generally, diabetic patients have higher BMD than nondiabetic one. However, they also have higher prevalence of fractures.[59] Some explanations suggest higher risk of falling and poor bone quality due to accumulation of advanced glycation end products (AGEs) on bone tissue.[60–62] This is a clear situation where high BMD does not prevent fractures. Moreover, structural alterations, such as osteoarthritis and disco-arthrosis of the spine or hip, can artificially increase bone density in these skeletal sites. This aspect should be considered in interpreting high BMD, especially in elderly individuals and patients with chronic and degenerative inflammatory joint diseases.[63]

Drugs

Several drugs have harmful effects on bone density, such as glucocorticosteroids, aromatase inhibitors, GnRH analogues, heparin and anticonvulvants. On the other hand, some medications are related to potential positive effect, such as thiazide diuretics and statins.

Thiazide diuretics are used for treating hypertension, idiopathic hypercalciuria and other conditions.[64] Randomized clinical trials have demonstrated higher bone density[64] and lower fractures rate[8] in current users *versus* non-users. These medications promote positive balance of calcium.[65] Besides, these drugs can also directly stimulate osteoblasts, regardless of their effects on the kidneys.[66]

Statins have shown conflicting results[67] primarily due to the pharmacokinetic and pharmacodynamic differences between them, such as hydrophilic (simvastatin and lovastatin) or lipophilic (pravastatin, atorvastatin and fluvastatin) characteristics.[68] Studying post-menopausal women with low bone density, Tanriverdi et al. have reported the synergic densitometric effect of atorvastatin when associated with bisphosphonates.[7]

However, Rejnmark found no significant differences in bone density of 82 postmenopausal women after 12 months follow-up.[69] Bone density is apparently unaltered by the use of simvastatin, pravastatin and atorvastatin.[70] Among those in which an important increase in bone density was found, there are reports of a longer administration of atorvastatin.[71] However, data on the anti-fracture ability of these drugs remain inconsistent,[68] although they have been shown to decrease biochemical bone markers.[72,73]

Simvastatin may enhance osteoblastogenesis through the stimulus of the production of bone morphogenetic protein (BMP-2)[74] and reduce osteoclastogenesis through inhibited production of farnesyl-diphosphate synthase.[75]

Hormone profile

Hormonal alterations play an important role on mineral and bone metabolism.[46]

Hormones related to obesity, such as leptin and pancreatic hormones, were discussed earlier.

Vitamin D and parathyroid hormone are discussed below.

Vitamin D and parathyroid hormone

Vitamin D and parathyroid hormone (PTH) are fundamental regulators of mineral and bone metabolism, especially with regard to intestinal absorption and renal resorption of calcium as well as bone formation and resorption.[46] Dietary vitamin D intake and adequate exposure to sunlight are necessary for the maintenance of plasma concentration of 25(OH)D.[3] There are few food sources that contain vitamin D and in spite of what occurs in other countries there is no dietary fortification in Brazil. Environmental (latitude, season of the year, ozone layer and cloud cover) and personal (skin type, clothing and use of sun block) factors are involved in the serum level of vitamin D and bone health. Deficiency of vitamin D causes secondary hyperparathyroidism and higher bone loss.[76]

Sex hormones

Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus and stimulates the secretion of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the anterior pituitary. In women, these hormones stimulate the ovarian production of estrogen and progesterone and inhibin which, in turn, regulates secretion of GnRH, FSH and LH through a feedback mechanism.[77] The loss of this mechanism, such as in menopause (hypoestrogenism), increases the plasma concentrations of FSH and LH, which have a negative effect on bone tissue.[78]

Several authors have demonstrated that a serum increase in FSH and reduction in inhibin lead to bone loss in perimenopausal women.[77] In contrast, a reduction in FSH is closely related to a gain in bone mass.[79] Assessing 699 healthy Chinese women between 20 and 82 years of age (464 in the pre-menopause period), Xu et al.[77] found that an increase in FSH and LH of 10 UI/L was associated to a 5.5% and 4.4% reduction in spine BMD, respectively. FSH has recently been reported to regulate bone metabolism through the direct and indirect stimulations of osteoclasts.[80,81] It also stimulates the production of TNF-α, with a consequent greater activation of osteoclastogenesis.[82] The role of LH in bone tissue remains unknown, but it is speculated that it may induce an increase in androgens.[81]

Lipid profile

Epidemiological studies investigate the association between low bone density and higher cardiovascular mortality, concomitant medication, associated diseases and traditional risk factors.[83,84] Although results are contradictory, several authors speculate the negative association between bone mass and hypercholesterolemia.[83-85] *In vitro* studies have shown that products from the oxidation of lipids and lipoproteins inhibit the differentiation and function of osteoblasts[85,86] probably mediated by the mevalonate pathway.[87]

Conclusions and implications

Considering the lack of available information on associated protective factors, further studies are needed in order to allow a better understanding of the clinical aspects and physiopathogenic mechanisms associated with higher BMD and bone health. A better understanding of these factors could be an important strategy for the implementation of prevention and treatment measures for patients with bone frailty especially related to osteoporotic fractures.

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Conflict of interest

The authors have no conflict of interest to declare.

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Artigo 2:

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Low fatness, reduced fat intake and adequate plasmatic concentrations of LDL-cholesterol are associated with high bone mineral density in women: a cross-sectional study with control group

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Abstract

Background: Several parameters are associated with high bone mineral density (BMD), such as overweight, black background, intense physical activity (PA), greater calcium intake and some medications. The objectives are to evaluate the prevalence and the main aspects associated with high BMD in healthy women.

Methods: After reviewing the database of approximately 21,500 BMD scans performed in the metropolitan area of São Paulo, Brazil, from June 2005 to October 2010, high BMD (over 1400 g/cm^2 at lumbar spine and/or above 1200 g/cm^2 at femoral neck) was found in 421 exams. Exclusion criteria were age below 30 or above 60 years, black ethnicity, pregnant or obese women, disease and/or medications known to interfere with bone metabolism. A total of 40 women with high BMD were included and matched with 40 healthy women with normal BMD, paired to weight, age, skin color and menopausal status. Medical history, food intake and PA were assessed through validated questionnaires. Body composition was evaluated through a GE-Lunar DPX MD + bone densitometer. Radiography of the thoracic and lumbar spine was carried out to exclude degenerative alterations or fractures. Biochemical parameters included both lipid and hormonal profiles, along with mineral and bone metabolism. Statistical analysis included parametric and nonparametric tests and linear regression models. $P < 0.05$ was considered significant.

Results: The mean age was 50.9 (8.3) years. There was no significant difference between groups in relation to PA, smoking, intake of calcium and vitamin D, as well as laboratory tests, except serum C-telopeptide of type I collagen (s-CTX), which was lower in the high BMD group ($p = 0.04$). In the final model of multivariate regression, a lower fat intake and body fatness as well a better profile of LDL-cholesterol predicted almost 35% of high BMD in women. (adjusted R2 = 0.347; $p < 0.001$). In addition, greater amounts of lean mass and higher IGF-1 serum concentrations played a protective role, regardless age and weight.

Conclusion: Our results demonstrate the potential deleterious effect of lipid metabolism-related components, including fat intake and body fatness and worse lipid profile, on bone mass and metabolism in healthy women.

Keywords: Bone mineral density, Body composition, Lipid metabolism, Diet, Mineral metabolism, Women

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Background

In recent years, the occurrence of high bone mineral density (BMD) has been observed in some individuals [1]. However, little is known about the prevalence, physiopathogenic aspects involved, associated risk factors or the clinical relevance of this entity in medical practice, including the possibility to be a variant of normality or be considered a disease itself, since it associates with some morbidities.

So far, there is controversy about the definition of individuals with high BMD, since the World Health Organization [2] criteria for classification of osteopenia and osteoporosis does not consider this condition. Thus, individuals with values above one standard deviation (SD) are considered as normal, regardless of the absolute value or the number of standard deviations above the unit.

Although there are few studies on this subject, most of them point out to the role of anthropometric data (overweight and obesity) [3] and demographics (males and black ethnicity) [4], as well as genetic factors (LRP5 mutations) [5], lifestyle habits (intense physical activity [6], higher calcium intake above 1500 mg/day and food or water with excess fluoride) [7,8], as the main factors positively associated with high BMD. Some medications such as statins [9] and thiazide diuretics [10] may also have a protective effect. In addition, patients with breast and endometrial cancer [11], type II diabetes mellitus [12] and athletes have higher BMD than healthy individuals [13].

Thus, a better understanding of these aspects can help to optimize the management of patients with osteoporosis as well as minimize the burden of osteoporotic fractures throughout the world.

The objective of this study was to identify the prevalence, as well as risk factors and protection associated with high BMD in healthy women, through cross-sectional study with control group.

Results

Clinical and nutritional data (mean ± SD) are listed in Table 1. The groups were matched for age, weight, BMI, smoking, fat mass and menopausal status. In both groups, the prevalence of overweight was high, but without significant difference between them. Nevertheless, women with high BMD had higher FFM and ALM ($p < 0.05$). Seven healthy control women (17.5%) and three (7.5%) of the high BMD group were classified as sarcopenic ($p = 0.31$).

In the high BMD group, the only significant correlations found were between femoral neck BMD and BF% ($r = -0.36$; $p = 0.02$), BF ($r = -0.45$; $p = 0.004$) and RSMI ($r = 0.35$; $p = 0.02$).

After the adjustment of food intake for energy, significant difference was obtained between the groups regarding the intake of protein and phosphorus, with greater levels in women with high BMD ($p < 0.05$). The mean daily consumption of lipids, carbohydrates and vitamin D was similar in both groups. The mean intake of macronutrients as well as phosphorus were within the DRI values proposed by the Food and Nutrition Board [14-16]. Conversely, the mean calcium and vitamin D intake were below the proposed recommendations (Table 1).

While no statistically significant difference of metabolic, hormonal and bone parameters was observed

Table 1 Anthropometric, clinical and nutritional data of the population, according to BMD

	HBMD (N = 40)	Healthy controls (N = 40)	p
Age (years)	50.9 (8.2)	51 (8.5)	0.989
Weight (kg)	64.3 (5.2)	61.7 (6.7)	0.052
Height (m)	1.58 (0.1)	1.57 (0.0)	0.241
BMI (kg/m²)	25.6 (2.4)	25.2 (2.6)	0.497
Age of menarche (years)	13.0 (2.4)	13.0 (1.4)	0.913
Parity	2.4 (1.4)	2.2 (1.3)	0.460
Smoking packets-year	16.7 (19.3)	26.2 (27.7)	0.290
TPA index (score)	7.6 (1.2)	7.9 (1.3)	0.412
Bone Mineral Density			
Lumbar spine (g/cm²)	1.408 (0.1)	1.209 (0.1)	< 0.001
T-score	1.9 (1.0)	0.2 (0.8)	< 0.001
Z-score	2.5 (1.1)	0.9 (0.9)	< 0.001
Femoral neck (g/cm²)	1.119 (0.1)	0.986 (0.08)	< 0.001
T-score	0.9 (0.9)	-0.2 (0.6)	< 0.001
Z-score	1.7 (0.6)	0.7 (1.0)	< 0.001
Total femoral (g/cm²)	1.166 (0.1)	1.043 (0.2)	< 0.001
T-score	1.4 (1.0)	0.2 (0.7)	< 0.001
Z-score	1.9 (1.1)	0.7 (0.7)	< 0.001
Body Composition			
FFM (kg)	36.4 (4.1)	34.4 (3.9)	0.029
ALM (kg)	16.1 (1.9)	15.0 (1.7)	0.007
RSMI (kg/m²)	6.3 (0.7)	6.1 (0.7)	0.278
Body fat (%)	39.4 (6.8)	40.5 (6.0)	0.433
Total body fat mass (kg)	24.0 (4.8)	23.6 (5.4)	0.740
Dietary Intake (day)			
Energy (kcal)	1697.3 (460.5)	1749.3 (575.9)	0.653
Protein (g)	74.2 (10.9)	67.0 (11.3)	0.005
Fat (g)	57.6 (11.9)	58.8 (14.9)	0.700
Carbohidrate (g)	235.1 (30.7)	238.7 (36.9)	0.637
Calcium (mg)	836.4 (249.8)	754.7 (219.7)	0.124
Phosphorus (mg)	1178.9 (178.8)	1068.2 (153.9)	0.004
Vitamin D (μg)	1.9 (2.2)	2.0 (1.4)	0.944

BMI Body Mass Index, *TFA* Total Physical Activity, *FFM* Total Fat-Free Mass, *ALM* Appendicular Lean Mass, *RSMI* Relative Skeletal Muscle Index, Nutrients adjusted to energy. T- student Test

Table 2 Metabolic, hormonal and biochemical parameters of the metabolism bone and mineral of the population study, according BMD

	HBMD (N = 40)	Healthy controls (N = 40)	p
Glucose (mg/mL)	94.2 (20.0)	88.4 (17.4)	0.17
Uric acid (mg/dL)	4.8 (1.4)	4.5 (1.1)	0.40
Cholesterol total (mg/dL)	192.0 (45.3)	205.5 (38.6)	0.16
LDL-Cholesterol (mg/dL)	114.0 (32.4)	124.0 (33.2)	0.18
HDL-Cholesterol (mg/dL)	58.4 (13.2)	60.9 (9.5)	0.33
VLDL-Cholesterol (mg/dL)	22.3 (11.3)	21.8 (10.3)	0.86
Triglyceride (mg/dL)	111.9 (57.6)	109.9 (51.3)	0.82
Leptin (ng/mL)	0.4 (0.2)	0.4 (0.2)	0.78
IGF-1 (ng/mL)	115.7 (53.1)	134.5 (56.6)	0.13
Total testosterone (ng/dL)	22.8 (9.9)	26.9 (16.6)	0.59
Prolactin (ng/mL)	13.3 (15.6)	8.0 (4.6)	0.14
FSH (mUI/mL)	55.7 (50.9)	72.6 (51.5)	0.15
LH (mUI/mL)	18.2 (2.9)	20.2 (3.2)	0.09
Serum alkaline phosphatase (U/L)	108.9 (57.7)	113.3 (74.2)	0.77
Serum total calcium (mg/dL)	9.2 (0.4)	9.3 (0.4)	0.06
Serum ionic calcium (mmol/L)	1.2 (0.1)	1.2 (0.1)	0.66
Serum magnesium (mg/dL)	2.0 (0.2)	2.0 (0.2)	0.84
Serum phosphorus (mg/dL)	3.5 (0.5)	3.6 (0.5)	0.49
Serum CTX (ng/mL)	0.16 (0.2)	0.24 (0.3)*	0.04
Serum Vitamin D (ng/mL)	33.0 (15.7)	29.9 (9.5)	0.28
Serum PTH intact (pg/mL)	31.5 (14.9)	31.6 (15.4)	0.97
Urinary sodium (mEq/24h)	140.8 (68.2)	151.0 (58.9)	0.50
Urinary phosphorus (mg/24h)	381.7 (347.1)	432.4 (368.2)	0.56
Urinary calcium (mg/24h)	110.1 (84.7)	109.4 (103.4)	0.98

IGF-1 insulin-like growth factor, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *CTX* carboxy-terminal collagen crosslinks; *Leptin, Prolactin, CTX and Vitamin D were transformed in log for performed the statistical analysis;* Student's t-test

between the groups, the serum concentration of total cholesterol was above the recommended values and more vitamin D insufficiency was found in the control group (Table 2). In this group, only four women (10%) reported 25-OH-D concentrations lower than 20 ng/mL.

In patients with high BMD, negative correlation was verified between femoral neck BMD and total cholesterol (r = -0.30; p = 0.01) and LDL-cholesterol (r = -0.39; p = 0.01). On the other hand, serum IGF-1 correlated positively with lumbar spine BMD (r = 0.36; p = 0.02). Similar correlation was also observed between 25-OH-D and RSMI (r = 0.33; p = 0.04) and leptin and BF (r = 0.44; p = 0.004). Bone resorption was lower in high BMD women ($p < 0.05$) than in controls (Table 2).

In the final multiple linear regression model, IGF-1 was positively correlated with lumbar spine BMD in women with high BMD after adjustments for age, weight, BMI, menopause, smoking, lean mass and fat and total energy of the diet. In contrast, LDL-cholesterol and body fatness associated negatively while RSMI and femoral neck BMD associated positively. Additionally, higher fat intake as well as greater serum phosphorus and iPTH had negative association with total body BMD (Table 3).

Table 3 Final model of multivariable regression using equations to estimate HBMD in women

Equations	R	R^2	p
Spine BMD = 1.305+(0.361)IGF-1	0.361	0.108	0.022
Femur BMD = 1.096-0.272(TBFM)-0.396(LDLC)+0.337(RSMI)	0.659	0.347	< 0.001
Total body BMD = 1.599-0.330(FI)-0.413(P)-(0.298)PTH	0.649	0.367	< 0.001

IGF-1 insulin-like growth factor, *TBFM* total body fat mass, *LDLC*, LDL-cholesterol, *RSMI*, relative skeletal muscle index, *BMD*, body mineral density, *FI* fat intake, *P* serum phosphorus, *iPTH* intact serum parathyroid hormone; Models adjusted for age, weight, height, BMI, smoking, lean mass, fat mass, energy intake and menopause

Discussion

Our results show that the prevalence of women with high BMD in the healthy general population is relatively low (2%) and that the main positive aspects are independently associated with IGF-1 and skeletal lean mass. Conversely, aspects related to fats, such as higher body fatness, increased plasmatic concentration of LDL-cholesterol and fat intake, are associated negatively with the BMD in these individuals.

To our knowledge, this is the first study that has identified the main risk factors and protection associated with high BMD in healthy women from the general population, including the three components of body composition and nutritional aspects, as well as biochemical, mineral and hormonal parameters.

It is important to note that there is still not a clear definition of high BMD by the scientific community. In the most recent (2007) official positions of the International Society for Clinical Densitometry (ISCD) [17], there are no cut-off points (T- or Z-score) to classify the patient with high BMD [18]. Some authors use Z-score above 2.5 DP [19] and others consider the absolute value of BMD (g/cm^2) in its largest interquartile range [1]. In this study, a T-score above + 2 SD, in the absence of fractures or other osteosclerosing disorders, was chosen for this classification. These values were defined in accordance with the premise that T-score values below - 2 SD are indicative of low BMD and increased risk of fractures [17]. Thus, T-score values above + 2 SD could be used to classify individuals with high BMD.

IGF-1 works in both bone formation and resorption [20] and thus plays a relevant role for the acquisition and maintenance of bone mass. Looking at our data of healthy adult women, there was significant association with high BMD, especially in trabecular bone, explaining

nearly 11% of the bone density variation in these individuals. Other authors have found similar results [21-23].

Although there is vast positive evidence of IGF on bone mass, its function should be better explored. Recently, Cohen et al. showed osteoblasts seem to be resistant to the IGF-1 effect in women with osteoporosis. Thus, it would not have a positive role and should be evaluated with caution [24]. Furthermore, Clemens & Karsenty, underscore osteocalcin as a regulator of glucose metabolism by means of insulin receptors present in osteoblasts, acting both on systemic glucose homeostasis and BMD increment [25].

Lean mass is the main component of body composition associated with BMD [26-29], in which mechanical stress [30] and mechanosensory signaling, promoted by osteocytes, are the most studied determinants [31]. These aspects have been partially confirmed by our results since physical activity, per se, was unable to explain high BMD in healthy women.

Most likely, the women with high BMD evaluated in our study had lower bone resorption rate, as suggested by the lower values of CTX when compared to healthy controls. In view of the negative correlation between this bone turnover marker and the RSMI ($r = -0.31$; $p = 0.05$), we suggest that the trophic role of muscle mass (pro formation), associated with lower bone resorption, resulted in a positive net effect on BMD. One of the possibilities to explain lower bone resorption in women with high BMD may be lower serum FSH- and LH-plasma concentrations ($p = 0.09$), which inherently can play a negative role on bone tissue [32,33].

Alternatively, there are conflicting studies on the role of fat mass on BMD [34,35], since body weight traditionally has a positive role on bone mass, especially with greater cortical and periosteal remodeling [35]. In our case, fat mass, including percentage and absolute values, played a negative role on femoral neck BMD, independent of body weight, hormonal variables (aromatization of estrone to estradiol), and adiposity type (gynecoid vs. android).

The physiopathogenic mechanisms involved with the deleterious role of body fatness on bone tissue are not fully known, but some authors believe that protective bone strength is most associated with dynamic loads, those found with lean and muscular mass, than with static, observed with fat mass [36]. Moreover, the proinflammatory state observed in individuals with obesity or with greater adiposity may be related to increased bone resorption and thus greater injury to bone health, introducing the new concept of lipotoxicity [37].

It is important to emphasize that, according to our data, there was positive correlation between BF and serum leptin concentrations, suggesting greater peripheral resistance to leptin and therefore to insulin. Recently, leptin has been pointed out as an important regulator of osteoclast differentiation, since it controls the expression of RANKL (receptor activator of nuclear factor kappa-B ligand) and CART (cocaine and amphetamine regulated transcript) [38].

Worse lipid profile, defined by LDL cholesterol, was another aspect negatively associated with femoral neck BMD in women with high BMD, emphasizing once again the participation of lipid metabolism on bone tissue [35]. Lipoprotein lipid oxidation is able to stimulate osteoclastogenesis [39], as well as the greater intake of fats, via RANKL expression on activated T lymphocytes [40]. Moreover, this oxidation may have a negative action on osteoblast differentiation and bone formation [41]. Recently, some authors have shown greater bone loss [42] and increase in resorption bone markers in patients with hypercholesterolemia [43].

Although the incidence of dyslipidemia in patients with osteoporosis is still not known, the atherogenic lipid profile is known to be significantly associated with lower bone density in postmenopausal women [44]. However, the use of statins does not seem to play a beneficial role on bone health [45].

Likewise, the daily intake of lipids was also a factor negatively associated with BMD, as previously reported by other authors [46]. The ingestion of large amounts of fat can negatively affect the absorption of calcium, prostaglandin synthesis and osteoclastogenesis. It also increases the oxidation of lipids [47]. In addition, the ingestion of large amounts of fat is related to the increased expression of adipocyte differentiation factors, in particular to PPAR-γ (peroxisome proliferator-activated receptor gamma) [48]. According to data from the Framingham Osteoporosis Study, high fat consumption can be harmful to bone mass, particularly in individuals with greater allelic variation in PPAR-γ [48]. In our study, no gene polymorphisms were evaluated. It is worth mentioning that the exclusion of obese women reinforces our findings, since, in all likelihood, they consumed even more fat. Thus, lipid consumption above DRI recommendations is able to negatively affect BMD.

Traditionally, higher concentrations of iPTH and phosphorus are associated with worse bone health, as observed in patients with chronic renal insufficiency. Our results show that this combination is associated negatively with BMD in patients with high BMD.

Surprisingly, no significant difference was observed in mean plasma concentrations of vitamin D between the groups. Accordingly, women had high BMD independent of vitamin D, while on the other hand there was positive interaction between vitamin D, lean mass and higher femoral neck BMD. The role of vitamin D receptor (VDR) in muscle cells [49] could explain these findings. Unfortunately, falls, muscle strength and physical

incapacity were not objectives of this study and further research is needed to better understand the interaction between these aspects.

Additionally, women with high BMD had higher intake of protein and phosphorus, after adjustments for energy. However, when adjusted for protein intake, there was no significant difference in the daily intake of phosphorus (1144 .1 ± 140.3 vs. 1103.6 ± 123.8 mg, p = 0.17) between the high BMD and control groups, respectively. Several epidemiological observations on protein intake confirm our results [50], although some have shown a negative role [51]. When observing the beneficial role of protein intake, it is important to note that the effect of the protein-induced acid load does not promote bone loss or urinary calcium [52]. In addition, protein intake is able to increase IGF-1 values by almost 30% [53] and thus provide beneficial effect on bone metabolism. The combination of these two latter aspects was observed in our study.

Conversely, when evaluating protein intake (g) adjusted for body weight (g/kg), there was no significant difference between groups (1.2 g/kg for high BMD vs. 1.1 g/kg in controls, p = 0.2), although both were above the recommendation for healthy individuals (0.8 g/kg).

The limitations of this study include the lack of evaluation of genetic markers, the lack of measurement of muscle strength and variables that quantify the state of oxidative stress, as well as the amount of fluoride in water or in food ingested and the type and the quantification of visceral fat.

The strengths of this study included the careful selection of the sampling procedures, excluding the risk factors traditionally associated with high BMD such as black ethnicity, obese individuals, athletes and patients infected by hepatitis C virus (HCV) or with degenerative alterations of the lumbar spine or hip. Moreover, results were strengthened with the inclusion of a control group matched for age, weight, fat mass, ethnicity, physical activity and smoking, which reduces various biases and confounding factors.

This study expands upon the scientific understanding of bone and mineral metabolism, since it includes new aspects of practical interest, such as body adiposity, lipid profile and fat intake, and the non-pharmacological handling of patients with bone fragility. Thus, beyond adapting the intake of calcium and vitamin D and stimulating resistance exercises for an individual with osteoporosis, the physician and nutritionist should also guide the lower intake of fats, encourage aerobic activities and improve the lipid profile of these individuals.

Conclusion

Thus, our results show that the main protection factors associated with high BMD in healthy women are IGF-1 plasmatic concentration, skeletal lean mass and intake of protein. On the other hand, body fatness, worse lipid profile and fat intake played a negative role.

Methods

Study design, sampling and patient selection

After reviewing the database of approximately 21,500 BMD scans performed in healthy women for any reason, from June 2005 to October 2010, were found 421 exams (1.96%) with high BMD. This information has been originated from the São Paulo metropolitan area, Brazil, including primary, secondary and tertiary hospitals as well as data from general practitioners.

Through convenience sampling and consecutively, exams with BMD values above 1400 g/cm^2 or T-score greater than + 2 SD at lumbar spine and/or above 1200 g/cm^2 or T-score greater than + 2 SD at femoral neck were eligible to this study. Furthermore, none of these sites could have osteopenia or osteoporosis [2] or previous fracture.

The control group included healthy women matched for age, weight and ethnicity. Besides, they had BMD values lower than 1400 g/cm^2 (T-score less than 1.99 DP) at lumbar spine and/or under 1200 g/cm^2 (T-score less than 1.99 DP) at femoral neck. Similarly, none of the sites could have osteopenia or osteoporosis [2].

Women aged below 30 and above 65 years, black people, pregnant and those with BMI higher than 29.9 kg/m^2 were excluded. Moreover, the presence of diseases associated with any nutritional imbalance or osteometabolic conditions, including renal, infectious, neoplastic, digestive, endocrinologic, rheumatic and cardiovascular diseases were not included. History of alcoholic consumption [54], dyslipidemia, chronic hepatitis C, hormone treatment and individuals using statins or thiazide diuretics also were not eligible for the study.

Of 421 women, 381 (90.5%) were excluded for not meeting the eligibility criteria, particularly obesity and black ethnicity. Thus, 40 (9.5%) women constituted the study group.

The study protocol was examined and approved by the Research Ethics Committee of the University of São Paulo (USP) (number: 0170/09) and Universidade Federal de São Paulo (Unifesp/EPM) (number: 0229/04) and the participants who agreed to participate in the study gave written informed consent.

Collection of clinical information

Standardized questionnaires were used to verify the demographic characteristics and medical history. Menopause was defined as more than 12 months since the last menstrual period [55].

Evaluation of food intake

Food intake was measured through a Food Frequency Questionnaire (FFQ), consisting of 62 food items and

validated in Brazil [56]. The FFQ was administered by a trained nutritionist and the information provided reflected the pattern of food intake for the last six months. Portion size was evaluated with the aid of a food portion photo set.

Dietsys software, version 4.0 (National Cancer Institute, Bethesda, MD), was used to calculate the daily nutritional intake of total energy (kcal/day), macronutrients and some micronutrients, including calcium, phosphorus and vitamin D. All nutrients were adjusted for energy. Phosphorus was also adjusted to protein intake according to the method proposed by Willett & Stampfer [57] and compared with the Dietary Reference Intakes (DRIs) recommendation from Food and Nutrition Board [14-16].

Evaluation of physical activity

Physical activity (PA) was assessed through the Baecke Questionnaire of Habitual Physical Activity [58]. This tool evaluates three PA's main components: work, sport and leisure. All the answers, with the exception of the occupation activity and the type of sport, were precoded on a scale of 5 points, with descriptors that range from never (1) to very often (5). The level of occupational activity was classified as low (1), medium (3) or high (5). The score of sport activities was calculated by the equation: [intensity code × duration code × year proportion code] × 1.25. If there was more than one sport practiced, the values were added. As a result, each component of PA can receive a maximum of five points, with a maximum score of 15. Each index was rounded to the nearest tenth of the unit or point.

Anthropometry

All individuals were measured and weighed on a standard balance beam scale (Filizola®), calibrated periodically, wearing light clothes and without shoes. Weight was measured to the nearest 100 g. Standing height was measured with the aid of a stadiometer (Filizola®) by a trained individual. Body mass index (BMI) was calculated by the ratio between weight (kg) and height, in meters squared (kg/m^2).

Assessment of body composition and bone mineral density measurements

BMD assessment was performed on the lumbar spine (L1-L4) and femoral neck (g/cm^2) by using dual energy X-ray absorptiometry (DXA), DPX MD + densitometer (GE-Lunar Radiation Corporation, Madison, WI, USA). A well-trained technician followed a standard protocol. Quality control was done daily and phantom cross-calibration three times per week. For premenopausal women, Z-score was used in compliance with International Society of Clinical Densitometry (ISCD) recommendations [21] and supported by the Brazilian Society of Clinical Densitometry (SBDens), a national regulatory agency [59].

Body composition was also measured by DXA. Total body fat mass was evaluated in absolute values as body fat (kg) and percentage (BF%). Lean mass was defined as fat free mass (FFM), with special emphasis to appendicular lean mass (ALM) and the relative skeletal muscle index (RSMI). For women aged over 50 years, sarcopenia was defined according to the classification of Baumgartner [60], in which RSMI values below two standard deviations relative to young healthy population or less than 5.45 kg/m^2, for women; indicative of that condition. For younger women, the criterion was not used. RSMI is the ratio of appendicular lean mass (kg) and height squared (m^2).

The coefficient of variation was 1.5% for the lumbar spine and total body and 2% for the femoral neck.

Radiographic evaluation

Radiographic evaluation of dorsal and lumbar spine in anteroposterior and lateral positions was performed by a rheumatologist blinded for clinical data and specific procedures of the protocol data in order to exclude vertebral degenerative processes, as well as other causes of high BMD, including bone metastases, Paget's disease, fracture or congenital deformities (Schmorl's nodes, severe scoliosis). The image acquisition protocol followed the recommendation of 120 cm for tube film distance and X-ray beams centered in T8 and L3, respectively.

Laboratory and biochemical analysis

All the blood samples were collected in the morning after twelve hours of fasting.

Metabolic and hormonal parameters included glucose and uric acid, both evaluated by calorimetry; total cholesterol, fractions and triglycerides by the Trinder method; insulin growth factor-1 (IGF-1) by chemiluminescence, leptin by ELISA (IBL International) and total testosterone by RIA. Prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by fluorometric method.

Bone and mineral metabolism were also measured. Bone formation was evaluated by alkaline phosphatase (ALP) activity through enzymatic-kinetic method. Bone resorption was assessed by serum C-terminal fragment of type-I collagen (CTX), through chemiluminescence. Serum total calcium, ionized calcium and magnesium were measured by colorimetric assay and serum phosphorus by UV mobility. Intact parathyroid hormone (iPTH) and 25-hydroxivitamin D (25-OH-D) were evaluated by electrochemiluminescence. Additionally, 24-hour urine was collected for measuring urinary calcium by colorimetric assay, as well as the fraction of sodium excretion (potentiometry) and phosphorus (UV mobility).

The classification of vitamin D sufficiency adopted was proposed by Dawson-Hughes [61].

Statistical analysis

The results were analyzed as mean ± SD. The Kolmogorov-Smirnov test was used to verify the normal distribution of variables. Data with non-normal distribution were transformed into logarithm. Mean differences between groups were assessed by Student's t-test. Categorical variables were analyzed by chi-square test of association. The correlation between variables was evaluated by parametric tests and Pearson correlation.

Multiple linear regression models were used to identify factors associated with high BMD, used as dependent variable. Clinical characteristics, food intake data, physical activity score, body composition measurements and concentrations of biochemical parameters were considered as independent. P-values of < 0.05 were considered significant. All analyses were performed with the aid of Statistical Package for the Social Sciences, version 16.5 for Windows (SPSS Inc., Chicago, IL).

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Authors' contributions

KSS performed the sample collection, nutritional assessments and processed the data, as well as conducted statistical analysis and drafted the manuscript. **VLS** and **LAM** participated in the design of the study and helped in analyzing data and in drafting the manuscript. **MMP** participated in the design of the study, performed medical appointment and BMD measurements and analyzed all spine X-ray exams. Additionally, he helped in data interpretation and in drafting of the manuscript. All authors have read and approved the final version.

Competing interests

No disclosures. There is no affiliation, financial agreement or any other involvement with any company.

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Artigo 3:

"The relationship between dietary patterns and high bone mineral density "

Artigo original à ser submetido

The Relationship Between Dietary Pattern and High Bone Mineral Density

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Abstract

Background: Several parameters are associated with high bone mineral density (BMD), among them the diet. The objective of the present study was to identify the differences between dietary pattern in women with normal and high BMD. **Methods:** After reviewing the database of approximately 21500 BMD scans performed in the metropolitan area of São Paulo, Brazil, from June 2005 to October 2010, high BMD (over 1400 g/cm^2 at lumbar spine and/or above 1200 g/cm^2 at femoral neck) was found in 421 exams. Exclusion criteria were age below 30 or above 60 years, afrodescendets, pregnant or obese women, disease and/or medications known to interfere with bone metabolism. A total of 40 women with high BMD were included and matched with 40 women with normal BMD, paired to weight, age, skin color and menopausal status. Medical history, diet and physical activity were assessed through validated questionnaires. Foods were systematically grouped together on the basis of similarities of food and nutrient composition and entered into factor analysis. Body composition was evaluated through a GE-Lunar DPX MD. Radiography of the thoracic and lumbar spine was carried out to exclude degenerative alterations or fractures. Statistical analysis included parametric tests and factor analysis. $P < 0.05$ was considered significant. **Results:** The mean age was 50.9 (8.3) years. There was no significant difference between groups in relation to age, weight, BMI, smoking, fat mass and menopausal status. Five components were identified through factor analysis that explained approximately 75% of the variability within the sample. The HBMD group had a healthier diet. Cereals, tubercles, beans, dairy products, fruit, vegetables, sweets, meats and eggs, with low of processed meat, explained more than 50% of the total variance. On the other in control group, diet was constituted with a

processed meat, food rich in fat and low alcoholic beverages, which differ the other group. **Conclusion:** Our results demonstrate the differences between dietary patterns in two different groups according to BMD. The HBMD group had a healthier, balanced dietary

Keywords: bone mineral density, body composition, dietary pattern, diet, women

Introduction

In recent years, the occurrence of high Bone Mineral Density (BMD) has been observed in some individuals [1] and it is related to anthropometric data (overweight and obesity) [2], demographics (african descendants), gender (males) [3], as well as genetic factors (LRP5 mutations) [4]. Some medications such as statins [5] and thiazide diuretics [6] may also have a protective effect. In addition, patients with breast and endometrial cancer [7], type II diabetes mellitus [8] and athletes have higher BMD than healthy individuals [9]. Apart from these, diets is an important factor since it has been observed that a calcium intake (above 1500 mg/day) and food or water with excess fluoride [10,11].

Diet is one of the important modifiable factors for the development and maintenance of bone mass, however, the most common approach, examines single nutrients or foods, may not adequately account for complicated interactions and cumulative effects. Because people consume diets consisting of a variety of foods with complex combinations of nutrients, rather than isolated nutrients, the examination of only single nutrients or foods could result in the identification of erroneous associations between dietary factors and disease [12].

The dietary patterns allow investigators to examine the whole diet. It may better account for the cumulative and interactive effects of foods and nutrients within the diet and is proposed to better reflect real-world dietary intake in relation to biomarker of disease. [13-15]. There are some studies about dietary pattern and BMD [12, 16-18], but anyone compared the dietary pattern in women with High BMD and health control with normal BMD, this results can help to optimize the management of patients with osteoporosis using a modifiable factor, the diet.

In this regard the objective of this study was to identify the differences between dietary pattern, according to BMD with high BMD in healthy women, through cross-sectional study with control group.

Methods

Study design, sampling and patient selection

After reviewing the database of approximately 21500 BMD scans performed in healthy women for any reason, from June 2005 to October 2010, 421 exams (1.96%) with high BMD were found. This information has been originated from the São Paulo metropolitan area, Brazil, including primary, secondary and tertiary hospitals as well as data from general practitioners.

Through convenience sampling and consecutively, exams with BMD values above 1400 g/cm^2 or T-score greater than + 2 SD at lumbar spine and/or above 1200 g/cm^2 or T-score greater than + 2 SD at femoral neck were eligible.

The control group included healthy women matched for age, weight and ethnicity. Besides, they had BMD values lower than 1400 g/cm^2 (T-score less than 1.99 DP) at lumbar spine and/or under 1200 g/cm^2 (T-score less than 1.99 DP) at femoral neck. Similarly, none of the sites could have osteopenia or osteoporosis [19].

Women aged below 30 and above 65 years, African descendants woman, pregnant and those with BMI higher than 29.9 kg/m^2 were excluded. Moreover, the presence of diseases associated with any nutritional imbalance or osteometabolic conditions, including renal, inflammation, neoplastic, digestive, endocrinologic, rheumatic and cardiovascular diseases were not included. History of alcohol consumption [20], dyslipidemia, chronic hepatitis C, hormone treatment and individuals using statins or thiazide diuretics also were not eligible for the study.

Of 421 women, 381 (90.5%) were excluded for not meeting the eligibility criteria, particularly obesity and african descendants. Thus, 40 (9.5%) women constituted the study group.

The study protocol was examined and approved by the Research Ethics Committee of the University of São Paulo (USP) (number: 0170/09) and Universidade Federal de São Paulo (Unifesp/EPM) (number: 0229/04) and the participants who agreed to participate in the study gave written informed consent.

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Standardized questionnaires were used to verify the demographic characteristics and medical history. Menopause was defined as more than 12 months since the last menstrual period [21].

Evaluation of food intake

Dietary intake information was collected using a quantitative Food Frequency Questionnaire (FFQ), consisting of 62 food items and validated in Brazil [22]. The FFQ was administered by a trained nutritionist and the information provided reflected the pattern of food intake for the last six months. Portion size was evaluated with the aid of a food portion photo set.

Foods were systematically grouped together on the basis of similarities of food and nutrient composition, thus reducing the 62 foods to 10 food groups. The following food groups were formed: food rich in fat (butter, margarine, olive oil, soybean oil, mayonnaise and mayonnaise salad); alcoholic beverages (fermented and distilled); non-alcoholic beverages (tea, coffee and soft drink); meat and eggs (beef, pork, poultry, fish, quail egg, chicken egg and omelet); processed meat (sausage, salami and ham); cereals and tubercles (rice, potatoes, bread, crackers, ,pasta, pastry, cassava and maize flour); sweets (deserts, cookies with filling, ice-cream, jam, chocolate and suggar); fruits and vegetables (banana, grape, orange, tangerine, papaya, apple, pear, watermelon, cantaloupe, mango, pineapple, guava, persimmon, natural fruit juice, lettuce, chard, tomatoes, cabbage, spinach, beets, carrots, cucumbers, peppers, eggplant, broccoli, cauliflower and soup vegetables); beans (beans, peas, lentils and soybean); dairy products (milk, yogurt and cheese).

Evaluation of physical activity

Since physical activity is a potent confounding factor. The level of physical activity (PA) was assessed through the Baecke Questionnaire of Habitual Physical Activity [23]. This tool evaluates three PA's main components: work, sport and leisure. All the answers, with the exception of the occupation activity and the type of sport, were precoded on a scale of 5 points, with descriptors that range from never (1) to very often (5). The level of occupational activity was classified as low (1),

medium (3) or high (5). The score of sport activities was calculated by the equation: [intensity code x duration code x year proportion code] x 1.25. If there was more than one sport practiced, the values were added. As a result, each component of PA can receive a maximum of five points, with a maximum score of 15. Each index was rounded to the nearest tenth of the unit or point.

Anthropometry

All individuals were measured and weighed on a standard balance beam scale (Filizola®), calibrated periodically, wearing light clothes and without shoes. Weight was measured to the nearest 100 g. Standing height was measured with the aid of a stadiometer (Filizola®) by a trained individual. Body mass index (BMI) was calculated by the ratio between weight (kg) and height, in meters squared (kg/m^2).

Assessment of body composition and bone mineral density measurements

BMD assessment was performed on the lumbar spine (L1-L4) and femoral neck (g/cm^2) by using dual energy X-ray absorptiometry (DXA), DPX MD + densitometer (GE-Lunar Radiation Corporation, Madison, WI, USA). A well-trained technician followed a standard protocol. Quality control was done daily and phantom cross-calibration three times per week. For premenopausal women, Z-score was used in compliance with International Society of Clinical Densitometry (ISCD) recommendations [24] and supported by the Brazilian Society of Clinical Densitometry (SBDens), a national regulatory agency [25].

Body composition was also measured by DXA. Total body fat mass was evaluated in absolute values as body fat (kg) and percentage (BF%). Lean mass was defined as fat free mass (FFM), with special emphasis to appendicular lean mass (ALM) and the relative skeletal muscle index (RSMI). For women aged over 50 years, sarcopenia was defined according to the classification of Baumgartner [26], in which RSMI values below two standard deviations relative to young healthy population or less than 5.45 kg/m^2, for women; indicative of that condition. For younger women, the criterion was not used. RSMI is the ratio of appendicular lean mass (kg) and height squared (m^2).

The coefficient of variation was 1.5% for the lumbar spine and total body and 2% for the femoral neck.

Radiographic evaluation

Radiographic evaluation of dorsal and lumbar spine in anteroposterior and lateral positions was performed by a rheumatologist blinded for clinical data and specific procedures of the protocol data in order to exclude vertebral degenerative processes, as well as other causes of high BMD, including bone metastases, Paget's disease, fracture or congenital deformities (Schmorl's nodes, severe scoliosis). The image acquisition protocol followed the recommendation of 120 cm for tube film distance and X-ray beams centered in T8 and L3, respectively.

Statistical analysis

The results were analyzed as mean ± SD. The Kolmogorov-Smirnov test was used to verify the normal distribution of variables. Mean differences between groups were assessed by Student´s t-test. P-values of < 0.05 were considered significant.

Dietary patterns were obtained by exploratory factor analysis of the ten food groups. The data was verified using the Kaiser-Meyer-Olkin (KMO) measurement of sample adequacy and the Barlett Test of Sphericity (BTS), wich tests the presence of correlations between variables [27].

The choice of the number of factor was first based on the Kaiser criterion, namely eigenvalues over 1.0. This is the most frequently used criterion in factor analysis, and the theoretical basis behind it is that each retained factor should explain more variance then the original variable in the data set. All analyses were performed with the aid of Statistical Package for the Social Sciences, version 16.5 for Windows (SPSS Inc., Chicago, IL).

Results

Table 1 presents the distribution of cases and controls according to BMD. The groups were matched for age, weight, BMI, smoking, fat mass and menopausal status. In both groups, the prevalence of overweight was high, but without significant

difference between them. Nevertheless, women with high BMD had higher FFM and ALM ($p < 0.05$).

The dietary pattern is demonstrated in **Table 2 and 3**, according to BMD. Five Components were identified through factor analysis, based on the Kaiser criterion. The observed KMO was 0.5 in both groups, indicating that the sample was considered to be adequate for factor analysis. These five components accounted for 75.4% and 75.1% of the variability within the sample in HBMD and health controls group, respectively.

The HBMD group had the first principal component, which accounted for 20% of the total variance. Cereals, tubercles and beans characterized this factor. On the other hand, foods rich in fat, processed meat, fruit and vegetables, were responsible for 21% of the total variance in healthy controls.

The second principal component explained 18% and 16.5% of the total variance in HBMD and health control, respectively. This factor was characterized by meats, eggs and dairy products in both groups. In addition fruit, vegetables and sweets are present in HBMD group; beans in health control with low consumption of alcoholic beverage.

The third principal component in HBMD was characterized by low consumption of processed meat, 15% of the total variance. In health control beans are the high factor loading, 14% of the total variance.

Foods rich in fat explained the fourth principal component in HBMD group (11.5%), while in health control cereals and tubercles explain 12.3% of the total variance. The fourth feature in health control is low consumption of sweets.

In fifth principal component it is worth noting the opposition to the results. While the HBMD women had low consumption of soft drinks, control group presents a high consumption of these drinks. This factor explained 10.2% and 10.9% of the total variance in HBMD and control group, respectively.

Discussion

To our knowledge, this is the first study using principal component analysis to compare dietary pattern in HBMD and normal BMD. Five patterns that explained approximately 75% of the total variability of diet in each group were identified.

The HBMD group appeared to had a healthier diet. Cereals, tubercles, beans, dairy products, fruit, vegetables, sweets, meats and eggs, with low processed meat, explained more than 50% of the total variance. These foods contain nutrients that are associated with bone health. On the other hand control group presented a dietary patterns constituted with a processed meat, food rich in fat and low alcoholic beverages, which differ the other group. Apart from these, fruit, vegetables, beans, dairy products, meat, eggs also were part of the dietary pattern.

The consumption of cereals and tubercles was found in PC1 in women with HBMD and in PC4 in control group. Tucker (2002), using cluster analysis in men and women aged 60-93 years, identified a dietary pattern rich in fruit, vegetables and cereal group with a highest BMD in men [28]. According to recommendation of DRIs, cereals should be the basis of a healthy diet, giving preference to the wholegrain [29].

Beans, meat and eggs are high in protein. It's one of the main components of the bone matrix, however the relationship between dietary protein and bone health is controversial. There is the hypothesized that animal protein provides a higher dietary acid load than does vegetable protein, and as a consequence bone is lost, perhaps as a result of increased calcium excretion and negative calcium balance induced by acid load. However, other studies have not supported an association of negative calcium balance with animal compared with vegetable protein sources [30, 31]. In general terms, protein intake has been associated with a bone benefit, as noted in two meta-analysis. The first has called the dietary acid–ash hypothesis of bone loss into question [32] and the second show that protein intake reduces bone resorption markers and has a small positive association with BMD and BMC [33].

According to Hardcastle, 2011 the decreased of bone resorption observed in 'healthy" dietary pattern, in a cross-sectional study with 3236 women, may be explained by eating foods that provide adequate protein [31]. According in ourr previous study protein intake was one of the protection factors associated with high BMD in healthy women [35]. In this study the vegetable protein was present in PC1, while the meat and eggs stood out in PC2, therefore there a greater contribution from vegetable protein in women with HBMD. Independent of the protein it is present in a positive manner in both groups.

The dairy products in both groups are present in PC2. Hardcaltle (2011) using principal components analysis, based on 35 food groups, reported a positive contribution of dairy products, excluding milks [31]. Mc Naughton (2011) identified a beneficial association of dietary pattern consisted of legumes, seafood, seed and nuts, wine, rice and rice dishes, and other vegetables and vegetables dishes. These data suggest that other dietary factors could contribute to bone density when there is a low calcium intake [16].

The *Framingham Osteoporosis Study*, using cluster analysis, reported lower femoral neck BMD in elderly men in association with the 'candy cluster', but not in women [28]. In our results the sweets are in PC2 in HBMD women and with low consumption in control group (PC4) and explain of 18% and 12.3% of variability, respectively.

Despite the high-fat foods are present in both groups they were significant only in the fourth component in HBMD women. In our previous study we found the fat intake had a negative role in HBMD women. [35].It has been shown that dietary patterns such as the Western dietary pattern identified in the Nurses' Health Study and those high in fats, processed meat, and other high-energy foods, were directly associated with inflammatory markers such as c-reactive protein and IL-6 [36-39]. Inflammatory markers such as C-reactive protein and IL-6 have previously been shown to be associated with low BMD and increasing bone loss [40-42].

Maybe the presence of fruit and vegetables was an important contributor in HBMD and a protective factor for the control group, which maintained bone mass within the normal range in our study. According to Hardcastle, 2011. a diet rich in fruit and vegetables may reduce bone resorption [31].These foods have a negative potential renal acid load, wich may be important for bone health [43]. Tucker (2002) in *Framingham Osteoporosis Study*, investigated older adults and identified a diet high in fruit, vegetable and cereals had significantly greater BMD in men, but not in women [28].

It´s interesting observed that processed meat in women with normal BMD appear in PC1 (21.2%) and in women with HBMD there are a lower intake of these in PC3 (15.4%). Okubo identified a dietary pattern including fish, fruits, and

vegetables, and low in meat and processed meat was associated with higher BMD in pre-menopausal Japanese women [12].

Increased intake of fruit, vegetables and low-fat dairy products is emphasized in the Dietary Approaches to Stop Hypertension, and a randomized trial based on this intervention was shown to reduced bone turnover, serum osteocalcin by 8-11% and C-terminal telopeptide of type I collagen by 16-18%, and low sodium intake reduced calcium excretion in the DASH diet and control groups and serum osteocalcin in the DASH group [44].

The non-alcoholic beverage had opposite results between the groups (PC5). The relationship with BMD is controversial. Okubo (2006) didn't found association between beverage pattern and BMD among Japanese women [12]. On the other hand Tucker (2006) in *Framingham Osteoporosis Study* found an intake of cola, but not of other carbonated soft drinks, is associated with low BMD in women [45]. In animal models caffeine may reduce BMD through the enhancement in osteoclastogenesis [46].

Factor analysis is the most commonly used method to date to derive dietary patterns. Uses the variations in food intakes that exist in a population to create factors, or latent variables, which are defined by the foods whose consumption is highly correlated with the factor [47]

Describing food intake in patterns may be particularly useful in developing counseling programs [48].

Dietary patterns were not measured directly, but relied on reported FFQ. The use of FFQ to estimate intakes is not without error; however, they are accepted as standard.

In our analysis we identified a healthier, balanced dietary with cereals, tubercles, beans, dairy products, fruit, vegetables, sweets, meats and eggs, with low of processed meat in women with high BMD. This dietary pattern could be a potential public policy strategies improving bone health.

Table 1: Anthropometric, clinical and body data of the population, according to BMD

	Healthy controls (N = 40)	HBMD (N = 40)	p
Age (years)	51 (8.5)	50.9 (8.2)	0.989
Weight (kg)	61.7 (6.7)	64.3 (5.2)	0.052
BMI (kg/m^2)	25.2 (2.6)	25.6 (2.4)	0.497
Age of menarche (years)	13.0 (1.4)	13.0 (2.4)	0.913
Smoking packets-year	26.2 (27.7)	16.7 (19.3)	0.290
TPA index (score)	7.9 (1.3)	7.6 (1.2)	0.412
Bone Mineral Density			
Lumbar spine (g/cm^2)	1.209 (0.1)	1.408 (0.1)*	<0.001
Femoral neck (g/cm^2)	0.986 (0.08)	1.119 (0.1)*	<0.001
Total femoral (g/cm^2)	1.043 (0.2)	1.166 (0.1)*	<0.001
Body Composition			
FFM (kg)	34.4 (3.9)	36.4 (4.1)*	0.029
ALM (kg)	15.0 (1.7)	16.1 (1.9)*	0.007
RSMI (kg/m^2)	6.1 (0.7)	6.3 (0.7)	0.278
Body fat (%)	40.5 (6.0)	39.4 (6.8)	0.433
Total body fat mass (kg)	23.6 (5.4)	24.0 (4.8)	0.740

Student's T Test

BMI: Body Mass Index; TFA: Total Physical Activity; FFM: Total Fat-Free Mass; ALM: Appendicular Lean Mass; RSMI: Relative Skeletal Muscle Index.

Table 2: The five components (dietary patterns) identified from the food frequency questionnaires using factor analysis in HBMD

Food Group	Dietary pattern				
	PC1 (scores)	PC2 (scores)	PC3 (scores)	PC4 (scores)	PC5 (scores)
Food rich in fat	0.176	0.352	0.156	0.775	0.287
Alcoholic beverages	-0.235	-0.359	0.472	0.050	0.241
Non-alcoholic beverages	0.384	0.068	0.468	0.404	-0.558
Meats and eggs	0.272	0.542	0.085	-0.181	0.628
Processed meat	0.251	-0.001	-0.794	0.119	0.051
Cereals and tubercles	0.866	0.175	0.026	-0.093	-0.100
Sweets	-0.245	0.590	-0.533	0.223	-0.235
Fruit and vegetables	-0.355	0.653	0.331	0.029	0.074
Beans	0.850	-0.062	0.064	-0.184	0.076
Dairy products	-0.084	0.663	0.201	-0.498	-0.308
Eigenvalues	2.022	1.801	1.543	1.154	1.020
% Explained variance	20.216	18.008	15.425	11.538	10.198

Factor Analysis

PC: Principal Component

Table 3: The five components (dietary patterns) identified from the food frequency questionnaires using factor analysis in healthy controls

Food Group	Dietary pattern				
	PC1 (scores)	PC2 (scores)	PC3 (scores)	PC4 (scores)	PC5 (scores)
Food rich in fat	0.617	0.344	-0.295	0.151	0.235
Alcoholic beverages	0.336	-0.605	0.202	0.434	0.111
Non-alcoholic beverages	0.475	0.324	-0.258	-0.321	0.554
Meats and eggs	-0.475	0.503	-0.257	0.278	0.370
Processed meat	0.753	-0.011	0.355	0.288	0.105
Cereals and tubercles	-0.312	0.385	0.462	0.568	0.243
Sweets	0.412	0.298	0.361	-0.502	-0.124
Fruit and vegetables	0.561	-0.030	-0.466	0.373	-0.306
Beans	0.179	0.550	0.586	0.018	-0.276
Dairy products	0.001	0.517	-0.315	0.213	-0.566
Eigenvalues	2.126	1.651	1.414	1.233	1.086
% Explained variance	21.262	16.513	14.144	12.333	10.864

Factor Analysis

PC: Principal Component

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6. CONSIDERAÇÕES FINAIS

A alta prevalência de osteoporose e de fraturas por fragilidade óssea a nível mundial ressalta a importância de buscar a prevenção e novas estratégias de tratamento. Atualmente, acreditamos que a densidade mineral óssea elevada e saúde óssea são importantes para a osteoporose. Portanto, a identificação de fatores envolvidos no aumento da densidade mineral óssea de aplicabilidade possível, em populações de risco, se mostra de grande relevância.

Existem diversos fatores etiológicos envolvidos na elevada densidade mineral óssea, sendo que dentre os fatores modificáveis encontram-se a composição corporal, o perfil lipídico e a alimentação.

O presente estudo observou que a massa magra esquelética apresentou-se como preditor positivo para a DMO do fêmur, estando significamente aumentada em mulheres com EDMO. Efeito contrário foi observado em relação à massa gorda e concentrações séricas de LDL-colesterol para o mesmo sítio. Além disso, o consumo de lipídios foi preditor negativo para DMO do corpo total.

Adicionalmente foi observado que um padrão alimentar saudável, composto por cereais, tubérculos, leguminosas, lácteos, hortaliças, doces, carnes e ovos com baixo consumo de carnes processadas e bebidas açúcaradas, bem como um consumo moderado de alimentos ricos em gordura é realizado por mulheres com EDMO.

Desta forma, podemos concluir que a adequação do perfil de lipídeos séricos, representado pelo LDL-colesterol, e o desenvolvimento da massa magra, através de atividade física assistida, seja de grande valia para incremento e manutenção da DMO. Em relação ao consumo alimentar acreditamos que e a adequação da alimentação como um todo seja necessária, principalmente preconizando a moderação para consumo de carnes processadas e alimentos ricos em gordura. Estes pontos deveriam ser considerados no planejamento e na implementação de ações preventivas em populações de risco para redução da massa óssea e até mesmo como forma de tratamento.

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8. ANEXOS

Anexo I : **TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO**

Título do Projeto: Fatores Nutricionais, Antropométricos e Hormonais Relacionados à Elevada Densidade Mineral Óssea.

Pesquisadora Responsável: Karin Sedó Sarkis

Este projeto tem o objetivo de estudar os aspectos relacionados à elevada massa óssea em indivíduos que realizaram densitometria óssea de rotina por qualquer motivo. Para tanto serão necessários realizar os seguintes procedimentos:

- Exame de sangue. A coleta de sangue será feita por uma enfermeira e todo material utilizado é descartável. Serão coletados 20mL de sangue.
- Coleta de urina de 24 horas. Esta coleta é feita pela senhora em sua casa. Toda a urina do dia deve ser coletada e guardada em garrafa de água, que deverá ser mantida em geladeira, conforme orientado. Agendaremos um dia para que a senhora leve a garrafa.
- Radiografia da coluna, normalmente conhecido como raio-x de coluna.
- Densitometria óssea. A senhora ficará deitada em uma máquina que irá medir a quantidade de ossos, gorduras e músculos que a senhora possui. Este exame é igual ao exame já realizado anteriormente.
- Responder a três questionários que serão aplicados pela pesquisadora sobre sua alimentação, atividade física e saúde.

Durante a execução do projeto pode ocorrer desconforto pela "picada da agulha" do exame de sangue e possível formação de hematoma (o local da "picada" poderá ficar roxo). Caso tenha qualquer dúvida entre em contato pelos telefones (11) 3061-7762 ou (11) 3061-7859 com Ligia / Karin. Os resultados serão entregues em dia e horário pré-agendados pela pesquisadora.

A senhora tem o direito de:

1. receber resposta a qualquer pergunta e esclarecimento sobre os

procedimentos, riscos, benefícios e outros relacionados à pesquisa;

2. retirar o consentimento a qualquer momento e deixar de participar do estudo;
3. não ser identificado e ser mantido o caráter confidencial das informações relacionadas à privacidade.
4. procurar esclarecimentos com o Comitê de Ética em Pesquisa da Faculdade de Saúde Pública da Universidade de São Paulo, no telefone 11 3061-7779 ou Av. Dr. Arnaldo, 715 – Cerqueira César, São Paulo - SP, em caso de dúvidas ou notificação de acontecimentos não previstos.

Declaro estar ciente do exposto e desejo participar do projeto.

São Paulo, _____de_____ de _____ .

Anexo II: INVESTIGAÇÃO DE FATORES DE RISCO PARA AVALIAÇÃO DA MASSA ÓSSEA

1- Identificação: Data: __/__/__

Nome: _____ Data Nasc. __/__/__ Idade___ Raça: _____ RGH: _____ Fone: _____

2- Dados antropométricos:

Peso (kg): ____ Altura (m): _____ IMC: _____ Peso aos 25 anos de idade (kg): __

3- Dados Ginecológicos:

- Idade da primeira menstruação ? _____ anos

- Você já usou pílula anticoncepcional por mais de 3 meses ? sim □ não □ não sei □

- Você já ficou algum período em sua vida sem menstruar antes da menopausa (exceto, se

gravidez) ? sim □ não □ não sei □

- Idade da última menstruação ? ____ anos Número de filhos: ____

- Você fez cirurgia para retirar o útero ? sim □ não □ não sei □ Idade ____ (anos)

E, para retirar os ovários (um ou os dois)? sim □ não □ não sei □ Idade ___ (anos)

• Você fez reposição hormonal após a menopausa ? sim □ não □ não sei □

• Se sim, quando iniciado, o período foi superior a 1 ano ? sim □ não □ não sei □

• Você amamentou ? sim □ não □ não sei □

• Se sim, quantas crianças você amamentou por mais que 3 meses ? ____

4- História Mórbida Pessoal:

HAS □ DM □ Fibromialgia □ Neoplasia □ _____ Doença GI □ _____

Doença Renal □ _____ Doença CV □ _____ DRAI □ _____

Doença Endócrina □ _____ Hepatite □ ___

• Você já usou as seguintes medicações:

Estatinas □ Diuréticos de alça □ ou tiazídicos □ Hormônios Anabolizantes □ PTH □

Bisfosfonatos □ SERMS □ Suplemento de Cálcio □ ou vitamina D □ Calcitonina □ Corticosteróides □

5- Dados familiares :

• Em sua família (pai, mãe, irmãos) existe história de fratura de qualquer osso após os 50 anos de idade? sim □ não □ não sei □

• Em sua família (pai, mãe e irmãos) existe alguém com osteoporose ?sim □ não □ não sei □

• Em sua família (pai, mãe e irmãos) existe alguém com obesidade ? sim □ não □ não sei □

6- História Pessoal:

• Você já teve alguma fratura ? sim □ não □ não sei □

• Se sim, em qual sítio esquelético, com que idade e qual foi o tipo de trauma ?

_____

• Você já fez dieta para perder peso ? sim □ não □ não sei □ Quanto foi a perda ?

____kg

• Você já fez dieta para ganhar peso ? sim □ não □ não sei □ Quão foi o ganho ?

____kg

• Você foi considerado obeso na infância ou adolescência ? sim □ não □ não sei □

7- Hábitos:

• Com que freqüência você bebeu no último ano ?

diariamente □ 5-6 d/sem □ 3-4 d/sem □ 1-2 d/sem □ < 1 d/sem □ nunca □

• Tipo de bebida: destilados □ _____ fermentados □ _____

• Você já ficou acamado por um período superior a 2 meses ? sim □ não □ não sei □

• Você fumou cigarro ou usou outras formas de fumo (cachimbo ou charuto)?

atualmente □ no passado □ nunca □

• Idade de início ? ____ anos; Se parou, com que idade ? ____ anos; N° de cigarros/dia ? __

Anexo III: AVALIAÇÃO DO CONSUMO ALIMENTAR

UNIVERSIDADE DE SÃO PAULO
FACULDADE DE SAÚDE PÚBLICA
DEPARTAMENTO DE NUTRIÇÃO

Questionário de Frequência de Alimentos

Nome:_____ Data____/_____/_____

Peso:_____Altura:_____Data nasc. __/__/__ - idade _____anos

Início da doença:_____

Iníclo da menopausa: _____Peso anterior:_____

Suplementos: Você toma algum suplemento vitamínico?

Tipo:_____ Freqüência:_____

Você mudou seus hábitos alimentares recentemente por algum motivo?

(1) não (4) sim, devido a osteoporose

(2) sim, para perda de peso (5) sim, para ganhar peso

(3) sim, por orientação médica (6) outro motivo:

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Leite e derivados									
Leite Tipo: ( )integral ( ) desnat ( ) semidesnat								1 copo (150 ml)	P M G E
Iogurte ou coalhada								1 copo (200ml)	P M G E
Queijo Minas – Ricota								1 fatia pequena (20g)	P M G E
Requeijão ( ) regular ( ) light								1 colher sopa (20g)	P M G E
Queijos Amarelos								2 fatias médias (30g)	P M G E
Queijo Ralado								1 colher sopa (15g)	P M G E
Manteiga								2 ponta faca (5 g)	P M G E
Margarina								2 ponta faca (5g)	P M G E
Sorvete Cremoso								2 bola (120g)	P M G E

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Frutas/sucos									
Banana								1 uni média (60g)	P M G E
Uva								1 cacho	P M G E
Laranja/mexerica								2 uni médias (180g)	P M G E
Mamão								1 fatia gde ½ papaya (180g)	P M G E
Maça/Pera								1 uni média (130g)	P M G E
Melânica /Melão								1 fatia média (150g)	P M G E
Manga								1 uni gde (220g)	P M G E
Abacaxi								2,5 fat médias (260g)	P M G E
Goiaba/Caqui								1 uni peq (60g)	P M G E
Suco Laranja Natural								1 copo (200 ml)	P M G E
Suco Caju/Maracujá								1 copo (200 ml)	P M G E
Outros									

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Vegetais									
Alface Acelga								3 folhas médias (30g)	P M G E
Tomate								1 un peque – 4 fatias	P M G E
Couve Espinafre coz								3 colh sopa (60g)	P M G E
Beterraba Cenoura crua/coz								4 fatias 2,5 col sopa (50g)	P M G E
Pepino Pimentão								2 col sopa (20g)	P M G E
Berinjela								2 col sopa	P M G E
Brocoli Couve Flor								2 ramos médios	P M G E
Sopa de legumes								2 conchas médias (260ml)	P M G E
Outros									

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Leguminosas									
Feijão								1 concha média (90g)	P M G E
Soja								2 colheres sopa	P M G E
Ervilha, lentilha								2 col sopa (60g)	P M G E
Outros									P M G E

	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Carnes/ Ovos									
Carne Boi coz, assada, grelhada								1 bife médio, 3 pedaços (100g)	P M G E
Churrasco								3 pedaços (100g)	P M G E
Frango, coz, assado, frito								3-4 pedaços médiso (120g)	P M G E
Peixe coz, assado, grelhado, frito								1 posta, 1 pedaço grande (100-120g)	P M G E
Lingüiça, salsicha, presunto, etc..								1 unidade, 1 gomo ou 2 fatias (40g)	P M G E
Ovos (coz, frito)								1 unidade média (60g)	P M G E
Outros									

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Pães e Biscoitos									
Pão francês, forma, integral, caseiro, doce								1 unidade ou (2 fatias 50g)	P M G E
Biscoito salgado ou doce sem recheio								5 a 6 unidades (30g)	P M G E
Biscoito doce com recheio								3 unidades (40g)	P M G E
Bolos e tortas								1 fatia média (50g)	P M G E
Outros									P M G E

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Arroz/Massas									
Arroz coz c óleo e temp								3-4 colheres sopa (90g))	P M G E
Batata/Mandioca coz, frita, assada								2colheres, 2-3pedaços (50-180g)	P M G E
Salada de maionese								3 colheres de sopa (90g)	P M G E
Batata doce								3 ped médios ou 1 unid média (90g)	P M G E
Abóbora								3 pedaços médios (90g)	P M G E
Farofa/ fa mandioca								2 colheres de sopa (30g)	P M G E
Cuscuz/pirão/canjica								1 ped médio (130g)	P M G E
Macarronada/lasanha								1 esc ½ prato (75g)	P M G E
Pastelarias (empada, coxinha, pastel, etc)								1 unidade – 1 pedaço médio (60g)	P M G E
Outros									

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Doces/ sobremesas									
Doce de frutas								1 pedaço médio (60g)	P M G E
Chocolates, bombom. Brigadeiros								2 unidades ou 1 barra (30g)	P M G E
Acúcar (café, chá etc...)								3 cl cha (12g)	P M G E
Outros doces									P M G E

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Bebidas									
Café								1 xícara gde (200 ml)	P M G E
Chá								1 xícara gde (200 ml	P M G E
Refrigerantes, regular ou diet								1 copo	P M G E
Cerveja/Vinho								1 lata (350ml) 2cálices (120ml)	P M G E
Pinga, whisky, vodka								2 doses (60ml)	P M G E

Alimento	Nunca	Menos De 1x mês	1 a 3X mês	1x por sem	2 a 4x sem	1x dia	2 ou mais x dia	Porção Média	Sua Porção
Molhos/ óleos									
Oleo (soja, milho, etc)								3 col sobremesa (15g)	P M G E
Azeite								2 fios (10ml)	P M G E
Katchup/ mostarda								1 col sopa (10g)	P M G E
Maionese								1 col sopa (15g)	P M G E

Anexo IV: AVALIAÇÃO DA ATIVIDADE FÍSICA

	Até os 18 anos	Dos 19 aos 35 anos	Após os 35 anos
Tipo			
Freqüência (h/ semana)			
Duração			

1) Qual tem sido sua principal ocupação? 1 3 5

---

2) No trabalho, eu sento: nunca/raro/algumas vezes/freqüente/sempre
1 2 3 4 5

3) No trabalho, eu fico em pé: nunca/raro/algumas vezes/freqüente/sempre
1 2 3 4 5

4) No trabalho, eu ando: nunca/raro/algumas vezes/freqüente/sempre
1 2 3 4 5

5) No trabalho, eu carrego carga pesada: nunca/raro/algumas vezes/freqüente/sempre
1 2 3 4 5

6) Após o trabalho, eu carrego carga pesada:
Muito freqüente/freqüente/algumas vezes/raro/nunca 5 4
3 2 1

7) No trabalho, eu suo: muito freqüente/freqüente/algumas vezes/raro/nunca 5
4 3 2 1

8) Em comparação com outros da minha idade, eu penso que meu trabalho é fisicamente:

Muito mais pesado/mais pesado/tão pesado quanto/mais leve/muito mais leve 5
4 3 2 1

9) Você pratica ou praticou esporte ou exercício físico nos últimos 12 meses: Sim/ Não

10) Qual esporte ou exercício você pratica ou praticou mais freqüentemente?

_____

- quantas horas por semana? <1 1< 2 2<3 3-4 >4
- quantos meses por ano? <1 1-3 4-6 7-9 >9

Se você faz ou fez um segundo esporte ou exercício físico, qual o tipo? 1 3 5

- quantas horas por semana? <1 1< 2 2<3 3-4 >4
- quantos meses por ano? <1 1-3 4-6 7-9 >9

10) Em comparação com outros da minha idade eu penso que minha atividade física durante as horas de lazer é: Muito maior/maior/a mesma/menor/muito menor 5 4 3 2 1

11) Durante horas de lazer eu suo: muito freqüente/freqüente/algumas vezes/raro/nunca 5 4 3 2 1

12) Durante as horas de lazer eu pratico esporte ou exercício físico:

Nunca/raro/algumas vezes/freqüente/muito freqüente 1 2 3 4 5

13) Durante as horas de lazer eu vejo televisão:

Nunca/raro/algumas vezes/freqüente/muito freqüente 1 2 3 4 5

14) Durante horas de lazer eu ando: nunca/raro/algumas vezes/freqüente/muito freqüente 1 2 3 4 5

15) Durante as horas de lazer eu ando de bicicleta:

Nunca/raro/algumas vezes/freqüente/muito freqüente 1 2 3 4 5

16) Durante quantos minutos por dia você anda a pé ou de bicicleta indo e voltando do trabalho, escola ou compras? <5/ 5-15/ 16-30/ 31-45/ >45 1 2 3 4 5

Total em minutos:

Lígia Araújo Martini

Bolsista de Produtividade em Pesquisa do CNPq - Nível 2

Graduação em Nutricao pelo Centro Universitário São Camilo - Campus Pompeia (1989), mestrado em Nutrição pela Universidade Federal de São Paulo (1993) e doutorado em Nutrição pela Universidade Federal de São Paulo (1998). Realizou Pós-Doutorado no USDA Jean Mayer Human Nutrition Research Center on Aging at Tufts Univeristy - Boston MA. Foi Pesquisador Associado nível 3 no Mineral Bioavailability Laboratory da mesma instituição entre 2000 e 2001. Atualmente é Professor Associado da Universidade de São Paulo. É Coordenadora do Programa de Pós-Graduação em Nutrição em Saúde Pública da USP (inicio em 2010). Faz parte do Nucleo de Pesquias em Alimentos e Nutrição - NAPAN- da USP. Atua como editor contribuite do Nutrition Reviews e revisor científico da Clinical Nutrtition, Annals of Nutrition and Metabolism, Arquivos Brasileiros de Endocrinologia e Metabologia, Cadernos de Saúde Pública entre outras. Tem experiência na área de Nutrição, com ênfase em Nutrição e Metabolismo, atuando principalmente nos seguintes temas: metabolismo mineral ósseo, vitamina D, sindrome metabólica, macadores bioquímicos da ingestão alimentar e da composição coporal

(Texto informado pelo autor)

Última atualização do currículo em 14/06/2012
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Certificado pelo autor em 14/06/12

Dados pessoais

Nome Lígia Araújo Martini

Nome em citações bibliográficas MARTINI, LA;Martini, L. A.;Martini, Lígia A.;Martini, Lígia Araújo

Sexo Feminino

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Formação acadêmica/Titulação

2008 Livre-docência.
Universidade de São Paulo, USP, Brasil.
Título: Metabolismo ósseo: uma abordagem nutricional, *Ano de obtenção:* 2008.
Palavras-chave: Avaliação Nutricional; densidade mineral ossea; doença óssea.

1998 - 2001 Pós-Doutorado .
Jean Mayer Human Nutrition Research Center On Aging At Tufts Univeristy.
Bolsista do(a): Fundação de Amparo à Pesquisa do Estado de São Paulo ,FAPESP ,Brasil .
Grande área: Ciências da Saúde / *Área:* Nutrição / *Subárea:* Bioquimica da Nutrição / *Especialidade:* Biodisponibilidade de Nutrientes.
Grande área: Ciências da Saúde / *Área:* Nutrição / *Subárea:* Bioquímica da Nutrição / *Especialidade:* Interaçao Gene Nutriente.

1994 - 1998 Doutorado em Nutrição (Conceito CAPES 5) .
Universidade Federal de São Paulo, UNIFESP, Brasil.
Título: Influencia dos fatores dieteticos sobre a massa ossea de pacientes litiasicos, *Ano de Obtenção:* 1998.
Orientador: Profa Dra Ita Pfeferman Heilberg.
Bolsista do(a): Coordenação de Aperfeiçoamento de Pessoal de Nível Superior ,CAPES ,Brasil .
Palavras-chave: dieta; densidade mineral ossea; litiase renal; hipercalciuria.
Grande área: Ciências da Saúde / *Área:* Nutrição / *Subárea:* Bioquímica da Nutrição.
Setores de atividade: Cuidado À Saúde das Pessoas.

1991 - 1993 Mestrado em Nutrição (Conceito CAPES 5) .
Universidade Federal de São Paulo, UNIFESP, Brasil.
Título: Avaliacao da ingestão de nutrientes litogenicos em pacientes litiasicos, *Ano de Obtenção:* 1993.
Orientador: Prof Dr. Nestor Schor.
Bolsista do(a): Fundação de Amparo à Pesquisa do Estado de São Paulo ,FAPESP ,Brasil .
Palavras-chave: dieta; litiase renal.
Grande área: Ciências da Saúde / *Área:* Nutrição / *Subárea:* Análise Nutricional de População.
Setores de atividade: Nutrição e Alimentação.

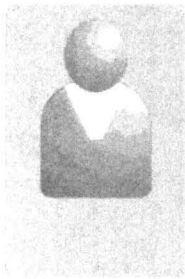
1985 - 1989 Graduação em Nutricao .
Centro Universitário São Camilo - Campus Pompeia, SAO CAMILO, Brasil.

Atuação profissional

Universidade de São Paulo, USP, Brasil.

Vínculo institucional

2001 - Atual Vínculo: Professor, Enquadramento Funcional: Professor doutor, Carga horária: 40, Regime: Dedicação exclusiva.



Karin Sedó Sarkis

Nutricionista. Doutoranda em Nutrição em Saúde Pública pela Faculdade de Saúde Pública - USP. Mestre em Saúde Pública, área de concentração Nutrição, pela Faculdade de Saúde Pública - USP. Nutricionista colaboradora do Ambulatório de Nutrição da Disciplina de Reumatologia - UNIFESP. Integrante da equipe do Check-up do Grupo Fleury Medicina e Saúde. Autora do livro Alimentação Saudável: a sua importância na qualidade de vida e na prevenção de doenças.
(Texto informado pelo autor)

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Nome Karin Sedó Sarkis

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Formação acadêmica/Titulação

2008 Doutorado em andamento em Nutrição .
FACULDADE DE SAÚDE PÚBLICA -UNIVERSIDADE DE SÃO, FSP, Brasil.
Título: Elevada massa óssea. Saúde ou doença?, *Orientador:* Dra. Lígia Araújo Martini.

2005 - 2007 Mestrado em Ciências da Saúde (Conceito CAPES 4) .
Universidade de São Paulo - Faculdade de Saúde Pública.
Título: Relação entre nutrientes,estado nutricional e metabolismo ósseo em mulheres com artrite reumatóide que apresentam ou não alteração na densidade mineral óssea, *Ano de Obtenção:* 2007.
Orientador: Dra. Lígia Araújo Martini.
Palavras-chave: artrite reumatóide; osteoporose; composição corporal; dieta.
Grande área: Ciências da Saúde / *Área:* Nutrição / *Subárea:* Nutrição em Doenças Ósseas.
Setores de atividade: Nutrição e Alimentação.

2001 - 2002 Especialização em Padrões Gastronômicos . (Carga Horária: 400h).
Universidade Anhembi Morumbi, UAM, Brasil.

1996 - 1999 Graduação em Nutrição .
Centro Universitário São Camilo - Campus Ipiranga.

Formação complementar

2009 - 2009 Aconselhamento em Alimentação Complementar. (Carga horária: 20h).
SECRETARIA DE ESTADO DA SAUDE.

2005 - 2005 IV Curso de Avanços e Tratamento da Osteoporose. (Carga horária: 10h).
Centro de Estudos em Doenças Ósteo-Metabólicas.

2005 - 2005 IX Curso Introdutório à Liga de Geriatria. (Carga horária: 15h).
Fundação Faculdade de Medicina.

2005 - 2005 Aperfeiçoamento ao Ensino. (Carga horária: 144h).
Faculdade de Saúde Pública - USP.

2004 - 2004 VII Curso Anual de Nefrologia. (Carga horária: 34h).
Fundação Faculdade de Medicina.

1999 - 1999 Aleitamento Materno. (Carga horária: 16h).
Hospital do Servidor Público Estadual.

1998 - 1998 Treinamento de Equipes Multiprof. em Amamentação. (Carga horária: 30h).
Faculdade de Ciências Médicas de Santos.

Atuação profissional

Universidade Nove de Julho, UNINOVE, Brasil.

Vínculo institucional

2011 - 2011 Vínculo: Professor Visitante, Enquadramento Funcional: Professor visitante (pós-graduação), Carga horária: 4

Outras informações Disciplina ministrada: Nutrição Clínica nos Diversos Ciclos da Vida do curso de Pós-graduação em Nutrição Clínica