表2　原発性骨粗鬆症の診断基準 改訂のポイント

①既存骨折種による分類を追加した（椎体・大腿骨近位部骨折，その他の骨折）。
②骨密度の測定部位は原則として腰椎または大腿骨近位部とした。
③大腿骨近位部骨密度の YAM は 20～29 歳を基準とした。
④骨密度は%表示と SD 表示を併記した（腰椎と大腿骨近位部について YAM の 70%と－2.5SD を併記）。
⑤腰椎骨密度測定部位として L1～L4 と L2～L4 を併記した。
⑥男性でも大腿骨近位部と腰椎の骨密度を用いることとした。
⑦デジタル化の普及を反映して脊椎エックス線像での骨粗鬆化の表記を削除した。
⑧QUS は採用しないこととした。
⑨国際基準と同様－2.5SD より大きく－1.0SD 未満の場合を骨量減少と定義した。
⑩重症骨粗鬆症と骨折の危険性の高い骨粗鬆症の条件について，本文で国内外のエビデンスを記載した。

ぐっては前回の診断基準から 10 年以上が経過したこともあり，コホート効果を考慮する必要性が指摘された。そこで日本骨代謝学会が集計した 1996 年と 2006 年の 20 歳以上の腰椎骨密度のデータを検証した結果，年齢や測定機種による大きな変動がなく，YAM に実質的な変化は認められなかった。一方，近年若年からの骨密度低下が認められる大腿骨近位部については，YAM 計算年齢を従来の 20～44 歳から 20～29 歳に変更することとした。

骨密度のカットオフ値については，骨折患者の検討結果に基づき YAM の 70%を採用してきたわが国に対して，WHO は閉経後女性の骨折ライフタイムリスクに基づき－2.5SD をカットオフ値として採用するなど，海外との不一致が問題点として指摘されてきた。今回，1996 年と 2006 年を合わせたデータの検討で，腰椎や大腿骨の YAM の 70%が－2.5SD とほぼ一致したことから，これらの部位のカットオフ値としては原則として－2.5 SD を採用することとなった。さらに，これまで骨密度が YAM の 70%以上 80%未満で，脊椎エックス線像で骨粗鬆化が疑われる場合に骨量減少としてきたが，先に杉本氏からも説明があったように，今回の改訂では骨折リスクが 2 倍以上に増加するカットオフ値－1.0SD を採用している海外と整合性をとり，「－2.5SD より大きく－1.0SD 未満」とする定義に変更された。

骨密度の評価部位については変形や高度の骨硬化を認める場合の扱いに課題を残すものの，腰椎では L1～L4 と L2～L4 を採用。大腿骨近位部では頸部とトータルを採用し，これらの部位の測定値の中で最も低い値を採用することとした。曽根氏は，評価部位については今回の改訂によって ISCD とほぼ同等の基準になった，としている。

予防と治療ガイドラインとの整合性

細井孝之氏からは「骨粗鬆症の予防と治療ガイドライン 2011 年版」と今回の改訂版診断基準の関連性と整合性をめぐって，特にガイドラインの薬物治療開始基準を中心に詳細な解説がなされた。

基本的に骨粗鬆症が診断された場合には薬物治療を検討すべきで，骨量減少例であっても高い骨折リスクを有する場合にはやはり薬物治療を考慮する必要がある。今回の診断基準ではガイドラインの薬物治療開始基準と同様に既存脆弱性骨折を骨折の強力な危険因子としてとらえており，骨折ハイリスク例を判別して骨粗鬆症性骨折を予防することが二つの基準に共通した目標であるといえる。細井氏はガイドラインの薬物治療開始基準のフローチャートを，改訂版診断基準によって診断される部分と，診断基準を補う情報とに分けて呈示した（図 1）。細井氏は，後者には糖尿病や CKD などの生活習慣病や続発性骨粗鬆症，骨代謝マーカーや転倒リスク，さらには患者の希望まで含まれるとし，骨粗鬆症の診断から薬物治療につながるこれらの要素を明確にしてコンセンサスを得る必要があることを強調した。

改訂版診断基準の完成に向けて

総合討論ではまず，診断基準に記載される「重症骨粗鬆症」と「骨折の危険性の高い骨粗鬆症」の説明について，医薬品の添付文書などと整合性

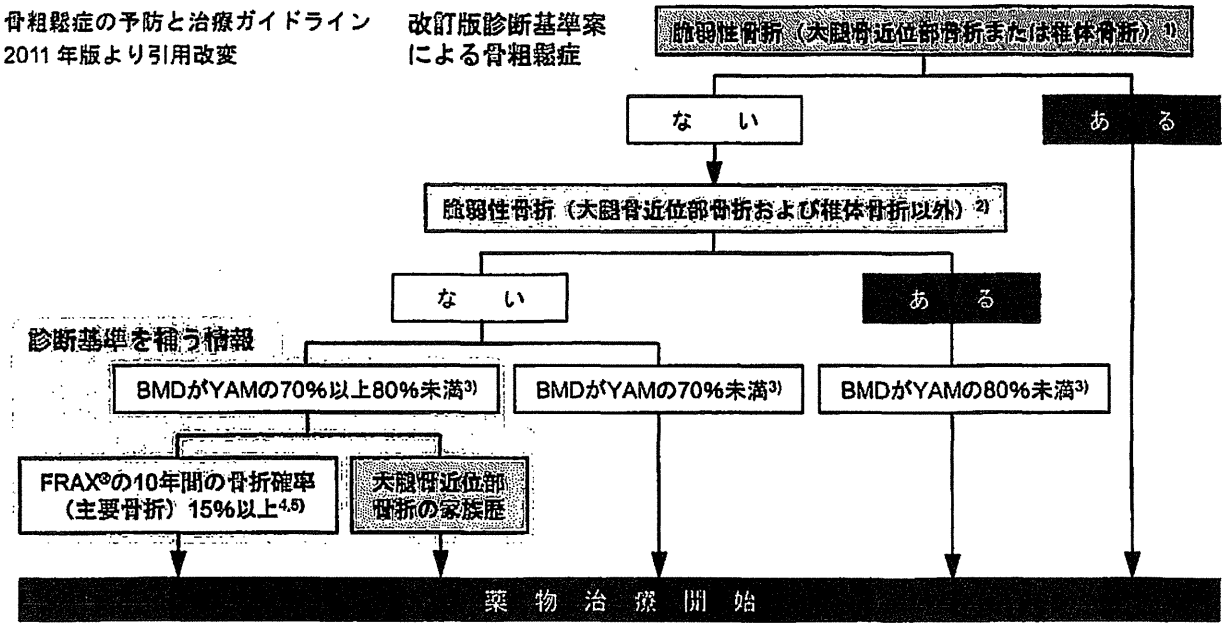

図 1　原発性骨粗鬆症の薬物治療開始基準と改訂版診断基準との関連性

1) 女性では閉経以降，男性では 50 歳以降に軽微な外力で生じた，大腿骨近位部骨折または椎体骨折をさす。
2) 女性では閉経以降，男性では 50 歳以降に軽微な外力で生じた，前腕骨遠位端骨折，上腕骨近位部骨折，骨盤骨折，下腿骨折または肋骨骨折をさす。
3) 測定部位によってはＴスコアの併記が検討されている。
4) 75 歳未満で適用する。また，50 歳代を中心とする世代においては，より低いカットオフ値を用いた場合でも，現行の診断基準に基づいて薬物治療が推奨される集団を部分的にしかカバーしないなどの限界も明らかになっている。
5) この薬物治療開始基準は原発性骨粗鬆症に関するものであるため，FRAX®の項目のうち糖質コルチコイド，関節リウマチ，続発性骨粗鬆症にあてはまる者には適用されない。すなわち，これらの項目がすべて「なし」である症例に限って適用される。

をとって現場での混乱を招くことのないよう検討されたいという意見が寄せられた。さらにわが国と海外の腰椎骨密度の SD 値が必ずしも一致しないことから，エビデンスとして記載された数値で判断するとハイリスクであっても治療対象とされないケースが出ることを危惧する意見も出た。これに対して杉本氏から重ねて，現状では WHO や国内外の臨床研究での評価をあくまでも参考として呈示するにとどめたものであるとのコメントがあり，続けて宗圓氏が，評議員から逆に「具体的な数値がないと基準として使いにくい」という要望が多く出されたために今回の対応となった，と説明した。

また，検診で広く使用されている QUS は治療効果の判定に優れているので，診断の補助的手段として取り入れられないかという意見が出された。宗圓氏は QUS が骨折リスク評価に優れ，ある程度骨密度との相関もあるので，スクリーニングにおける QUS の意義を認めないわけではないが，骨粗鬆症の診断はあくまでも骨密度によって行われるべきというのが委員会の考えであり，現状では QUS は採用できないとした。

骨密度の測定部位をめぐっては L1～L4 と L2～L4 を併記すると後者の意義が低くなってしまうのではないかとする意見も出たが，曽根氏は測定機器の精度も向上しており，基本的に世界標準である L1～L4 を測定してほしいが，引き続き L2～L4 の測定値でもデータとしては問題ないと答え，変形などで異常値が認められ判定が困難な場合は大腿骨近位部骨密度を採用して対応してほしいとつけ加えた。

改訂版診断基準は，今回のシンポジウムで寄せられたパブリックコメントについて検討を行い，その後に最終版が公表される。今学会のシンポジウムで議論された椎体骨折判定基準の改訂と併せて，近い将来，新しい基準と予防と治療ガイドラインの整合性をとるための検討も行われるものと思われる。

VAT53C019A
2012年11月作成

Clin Rheumatol
DOI 10.1007/s10067-013-2216-4

BRIEF REPORT

Prevalence of and factors associated with vitamin D deficiency in 4,793 Japanese patients with rheumatoid arthritis

Takefumi Furuya · Takayuki Hosoi · Eiichi Tanaka · Ayako Nakajima · Atsuo Taniguchi · Shigeki Momohara · Hisashi Yamanaka

Received: 1 October 2012 / Revised: 1 February 2013 / Accepted: 7 February 2013

Abstract To determine the prevalence of vitamin D deficiency and associations with clinical characteristics in Japanese patients with rheumatoid arthritis (RA), serum 25(OH)D levels, laboratory data, and clinical data were obtained from 4,793 patients with RA (4,075 women, 718 men, mean age 59.7 years) who participated in the Institute of Rheumatology Rheumatoid Arthritis observational cohort study in April and May of 2011. Serum vitamin D levels were evaluated using a radioimmunoassay. We defined vitamin D deficiency as <20 ng/mL and severe deficiency as <10 ng/mL. Associations of vitamin D deficiency with patient characteristics were examined using multivariate logistic regression. Among all patients, the mean (SD) serum 25(OH)D level was 16.9 ng/mL (6.1), and the prevalence of vitamin D deficiency and severe deficiency were 71.8 and 11.5 %, respectively. In multivariate analysis, female gender, younger age, high Japanese version of health assessment questionnaire (HAQ) disability score, low serum total protein levels, low serum total cholesterol levels, high serum alkaline phosphate (ALP) levels, and non-steroidal anti-inflammatory drug (NSAID) use were significantly associated with vitamin D deficiency ($P<0.01$). Vitamin D deficiency appears to be common in Japanese patients with RA, as previously reported for patients of other ethnicities. Female gender, younger age, high HAQ disability score, low serum levels of total protein and total cholesterol, high serum ALP levels, and NSAID use appear to be associated with vitamin D deficiency in Japanese patients with RA.

Keywords Disability · Japanese · Rheumatoid arthritis · Vitamin D deficiency

Introduction

Vitamin D (25[OH]D) deficiency is reported to be common in patients with rheumatoid arthritis (RA) [1–9]. Low vitamin D (25[OH]D) levels are also reported to be associated with disease activity [3–7, 10], physical disability [4, 6, 7, 10], and cardiometabolic intermediates [11] in patients with RA. Recent meta-analysis suggests that low vitamin D intake is associated with an elevated risk of RA development [12].

Among Japanese patients with RA, mean serum 25(OH)D levels of 80 patients were reported [13]. However, there are limited reports concerning prevalence of and factors associated with vitamin D deficiency in the literature on Japanese patients with RA.

Previously, we utilized data from our prospective, observational study of RA in Japan (IORRA, Institute of Rheumatology Rheumatoid Arthritis) to report clinical risk factors for fractures [14–16] and falls [17] in Japanese patients with RA. In this study, we examined the prevalence of 25(OH)D deficiency and associations with clinical characteristics in Japanese patients with RA.

T. Furuya (✉) · E. Tanaka · A. Nakajima · A. Taniguchi · S. Momohara · H. Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku 162-0054, Tokyo, Japan
e-mail: furuyat@ior.twmu.ac.jp

T. Hosoi
Department of Clinical Research and Development, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu City 474-8511, Aichi, Japan

Published online: 20 February 2013

Materials and methods

Patients

The IORRA cohort was established in October 2000 as a single institute-based large observational cohort of Japanese RA patients conducted at the Institute of Rheumatology, Tokyo Women's Medical University. Details regarding the study's purpose and methodology have been reported previously [14–18]. In this study, we analyzed patients who participated in the 22nd IORRA survey in April and May 2011. In brief, patients diagnosed with RA were registered into the IORRA cohort after informed consent was obtained, and they were required to complete and submit a survey biannually. Evaluated parameters included 28-joint disease activity score (DAS28), patient assessment of pain and global evaluation by the visual analogue scale (VAS) and disability measured by the Japanese health assessment questionnaire (J-HAQ) disability score [18]; physician evaluation of disease activity (swollen joint count, tender joint count, and physician's assessment by VAS); and the following clinical parameters: erythrocyte sedimentation rate (ESR), serum levels of C-reactive protein (CRP), rheumatoid factor (RF), total protein, creatinine, alkaline phosphatase (ALP), and total cholesterol. Patients also self-reported the use of non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), biologics, corticosteroids, bisphosphonates, and active vitamin D_3 analogues.

25(OH)D measurement

Patients were asked to undergo measurement of their serum levels of 25(OH)D vitamin D in the 22nd IORRA survey in April and May 2011. Patients who did not participate were excluded from this study. The DiaSorin 25(OH)D ^{125}I radioimmunoassay kit was used for quantitative determination of 25(OH)D in serum [1, 2, 5]. We defined vitamin D deficiency and severe deficiency as 25(OH)D serum level less than 20 ng/mL [19] and 10 ng/mL, respectively. A total of 5,162 patients with inflammatory polyarthritis were enrolled into this 22nd IORRA survey. Among these, 227 patients were excluded from this study because they did not want to undergo measurement of serum vitamin D levels, and 142 were excluded because they did not meet the 1987 classification criteria for RA developed by the American College of Rheumatology.

Statistical analysis

Chi-square tests and Wilcoxon rank-sum tests were used to compare categorical and continuous variables.

Spearman's rank correlation coefficient was used to find correlations between continuous variables. Associations of 25(OH)D levels below 20 ng/mL with patient characteristics were examined using multivariate logistic regression with stepwise regression models. Gender, age, body mass index (BMI), disease duration of RA, present or past smoking, J-HAQ disability score, DAS28, patient general VAS, patient pain VAS, physician global VAS, swollen joint counts, tender joint counts, ESR, RF positivity, serum levels of CRP, RF, total protein, creatinine, ALP, and total cholesterol, uses of NSAIDs, MTX, biologics, bisphosphonates, and active vitamin D_3 analogues, daily prednisolone dose, and weekly MTX dose were considered in the multivariate logistic regression analysis. $P<0.01$ was considered significant. All statistical analyses were conducted using JMP statistical software (Japanese version 7, SAS Institute, NC, USA).

Results

Demographic and disease-specific characteristics of all study participants (and patients with and without vitamin D deficiency) are shown in Table 1. Overall, 71.8 % (n= 3,443) and 11.5 % (n=552) of participants were deficient (<20 ng/mL) and severe deficient (<10 ng/mL), respectively. The mean (SD) vitamin D level for the entire group was 16.9 ng/mL (6.1). Patients with vitamin D deficiency were significantly younger, more likely to be female, had lower body weight and BMI, higher J-HAQ disability scores, patient pain VAS, patient general VAS, physician global VAS, lower total cholesterol levels, lower serum creatinine levels, tended to take NSAIDs, MTX, biologics, corticosteroid, and had higher daily prednisolone doses and weekly MTX doses, compared with those with vitamin D ≥20 ng/mL. DAS28 and active vitamin D_3 use were not significantly different between the two groups.

Table 2 shows vitamin D levels and prevalence of vitamin D deficiency (<20 ng/mL) by age and gender. Female patients had significantly lower vitamin D levels and were more likely to be vitamin D deficient in all age groups. In men and women with RA, younger patients tended to have lower vitamin D levels and greater prevalence of deficiency. In men, serum vitamin D levels were significantly different among patients in their 60s compared to those in their 70s. Among women, serum vitamin D levels were significantly different between patients in their 40s and those in their 50s, and between patients in their 50s and those in their 60s.

Spearman correlations between serum vitamin D levels and continuous variables are shown in Table 3. In unadjusted analysis, vitamin D levels were significantly associated with age, BMI, ESR serum levels of total cholesterol, and creatinine, and significantly inversely correlated with J-HAQ disability score, patient pain VAS, general VAS, physician global VAS, daily prednisolone dose, and weekly MTX dose among all patients, and

Table 1 Patient characteristics of Japanese patients with rheumatoid arthritis: total study population and among patients with and without 25(OH)-vitamin D deficiency (<20 ng/mL); data are percentages or medians (quartiles)

Characteristics	All participants n=4,793	With vitamin D Deficiency n=3,443	Without vitamin D Deficiency n=1,350	P[a]
Sociodemographics and health measures				
Age, years	61.7 (51.6, 69.3)	60.1 (48.7, 68.3)	64.5 (58.3, 70.7)	<0.0001
Women	85.0 %	88.2 %	76.3 %	<0.0001
Past or present smoker	33.0 %	32.4 %	34.5 %	0.194
Height, cm	157 (152, 162)	157 (152, 162)	157 (152, 162)	0.555
Weight, kg	52 (47, 58)	51 (46, 58)	52 (47, 60)	0.0004
BMI, kg/m^2	21.0 (19.2, 23.1)	20.8 (19.2, 23.0)	21.4 (19.5, 23.4)	<0.0001
Clinical measures				
Disease duration, years	12 (6, 19)	12 (6, 19)	12 (6, 20)	0.237
DAS28	2.9 (2.2, 3.7)	3.0 (2.2, 3.7)	2.9 (2.2, 3.6)	0.074
J-HAQ disability score (0–3)	0.4 (0, 1.1)	0.5 (0, 1.1)	0.3 (0, 1.0)	<0.0001
Patient pain VAS, cm	1.9 (0.6, 4.4)	2.0 (0.7, 4.6)	1.5 (0.5, 3.7)	<0.0001
Patient general VAS, cm	2.2 (0.8, 5.0)	2.3 (0.8, 5.0)	1.9 (0.6, 4.5)	<0.0001
Physician global VAS, cm	0.9 (0.2, 2.1)	1.0 (0.2, 2.1)	0.7 (0.1, 1.9)	0.0002
Swollen joint count (0–28)	0 (0, 1)	0 (0, 2)	0 (0, 1)	0.0013
Tender joint count (0–28)	0 (0, 2)	0 (0, 1)	0 (0,1)	0.032
ESR, mm/h	22 (12, 39)	22 (12, 38)	24 (13, 39)	0.026
RF–positive (>20 IU/mL)	71.7 %	72.0 %	70.9 %	0.454
Serum levels				
RF, IU/mL	50 (17, 119)	51 (18, 119)	48 (17, 119)	0.491
CRP, mg/100 mL	0.14 (0.04, 0.57)	0.13 (0.04, 0.55)	0.15 (0.05, 0.59)	0.011
Total protein, g/100 mL	7.2 (6.9, 7.6)	7.2 (6.9, 7.6)	7.3 (7.0, 7.6)	0.0783
TC, mg/100 mL	205 (182, 227)	203 (180, 226)	207 (186, 231)	<0.0001
Creatinine, mg/100 mL	0.63 (0.55, 0.73)	0.62 (0.55, 0.71)	0.66 (0.58, 0.79)	<0.0001
ALP, IU/L	245 (199, 301)	245 (199, 303)	245 (199, 298)	0.969
Medications				
NSAID use	54.1 %	56.7 %	47.6 %	<0.0001
MTX use	71.7 %	72.9 %	68.7 %	0.032
Biologic use	14.9 %	16.4 %	11.2 %	<0.0001
Corticosteroid use	38.5 %	40.0 %	34.9 %	0.0012
Bisphosphonate use	23.6 %	23.5 %	23.9 %	0.791
Active vitamin D_3 use	10.6 %	10.2 %	11.4 %	0.230
Daily prednisolone dose, mg/day	0 (0, 3)	0 (0, 3)	0 (0, 2)	0.0004
Weekly MTX dose	6 (0, 10)	6 (0, 10)	6 (0, 8)	<0.0001

BMI body mass index, *DAS28* 28-joint disease activity score, *J-HAQ* Japanese health assessment questionnaire, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor, *CRP* C-reactive protein, *ALP* alkaline phosphate, *TC* total cholesterol, *NSAID* non-steroidal anti-inflammatory drug, *MTX* methotrexate

[a] Between with and without vitamin deficiency

among patients with and without DAS28 <2.6. Among all patients and among patients with DAS28 <2.6, vitamin D levels were significantly associated with both weight and serum CRP levels. Vitamin D levels were significantly inversely correlated with DAS28 only in patients with DAS28 ≥2.6.

Results of multivariate analysis are shown in Table 4. Female gender, age, J-HAQ disability score, serum total protein levels, serum total cholesterol levels, serum ALP levels, and NSAID use were significantly associated with risk of vitamin D deficiency (P<0.01). Although not statistically significant, past or present smoking (P=0.025) and

Table 2 Vitamin D levels and deficiency (<20 ng/mL) by age in Japanese men and women with rheumatoid arthritis: data are averages (SD) and numbers (percent)

Age (years)	Number	Male		Number	Female	
		Vitamin D levels	Deficiency		Vitamin D levels	Deficiency
<40	48	16.7 (5.9)	33 (68.8 %)	420	13.9 (5.1)	368 (87.6 %)
40s	66	16.8 (5.7)	47 (71.2 %)	546	14.2 (5.0)	477 (87.4 %)
50s	149	17.9 (6.4)	97 (65.1 %)	892	16.1 (5.3)	694 (77.8 %)
60s	244	19.6 (6.5)	130 (53.3 %)	1,331	17.8 (6.2)	888 (66.7 %)
70s	165	21.8 (6.5)	70 (42.4 %)	743	17.5 (6.1)	510 (68.6 %)
≥80	46	19.3 (6.7)	29 (63.0 %)	143	17.1 (5.2)	101 (70.6 %)
Total	718	19.3 (6.6)	405 (56.4 %)	4,075	16.5 (5.9)	3,038 (74.6 %)

daily prednisolone dose (P=0.019) appeared to be associated with vitamin D deficiency, DAS28 was not significantly associated with vitamin D deficiency in the multivariate analysis.

Discussion

In this study, more than 70 % of Japanese patients with RA (56 % in men and 75 % in women) were vitamin D deficient (Tables 1 and 2). This finding is in agreement with previous reports on patients of other ethnicities with RA [1–9]. The Japanese rheumatologists should recognize that vitamin D deficiency is common in Japanese patients with RA as well as among RA patients of other ethnicities.

We observed a significant association of vitamin D deficiency with female gender and younger age (Tables 1, 2, 3, and 4). Previous studies have shown that RA patients with vitamin D deficiency are more likely to be female [1, 5], and we confirmed this in Japanese patients with RA. Ohta et al. reported that vitamin D deficiency is common and that lifestyle factors affect vitamin D levels in young Japanese women [20]. Nakamura reported that vitamin D intake is lower in young women than in middle-aged and/or elderly

Table 3 Unadjusted associations between serum 25(OH)D levels and continuous variables in Japanese patients with rheumatoid arthritis

Characteristics	All patients[a] n=4,793	DAS28 <2.6 n=1,817	DAS28 ≥2.6 n=2,958
Age, years	0.24 (<0.0001)	0.26 (<0.0001)	0.23 (<0.0001)
Height, cm	−0.0082 (0.57)	0.048 (0.043)	−0.045 (0.016)
Weight, kg	0.069 (<0.0001)	0.15 (<0.0001)	0.021 (0.26)
BMI, kg/m^2	0.085 (<0.0001)	0.15 (<0.0001)	0.049 (0.0086)
Disease duration, years	0.031 (0.039)	0.018 (0.46)	0.043 (0.022)
DAS28	−0.031 (0.032)	0.019 (0.41)	−0.060 (0.0010)
J-HAQ disability score (0–3)	−0.093 (<0.0001)	−0.096 (<0.0001)	−0.092 (<0.0001)
Patient pain VAS, cm	−0.092 (<0.0001)	−0.10 (<0.0001)	−0.10 (<0.0001)
Patient general VAS, cm	−0.073 (<0.0001)	−0.080 (<0.0001)	−0.085 (<0.0001)
Physician global VAS, cm	−0.072 (<0.0001)	−0.051 (<0.0001)	−0.086 (<0.0001)
Swollen joint count (0–28)	−0.068 (<0.0001)	−0.062 (0.0084)	−0.042 (0.024)
Tender joint count (0–28)	−0.035 (0.017)	−0.020 (0.40)	−0.078 (<0.0001)
ESR, mm/h	0.040 (0.0058)	0.070 (0.0030)	0.052 (0.0044)
CRP, mg/100 mL	0.055 (0.0001)	0.12 (<0.0001)	0.041 (0.025)
RF, IU/mL	−0.021 (0.14)	−0.0047 (0.84)	−0.025 (0.18)
Total protein level, g/100 mL	0.037 (0.011)	0.064 (0.0068)	0.023 (0.22)
TC level, mg/100 mL	0.094 (<0.0001)	0.11 (<0.0001)	0.081 (<0.0001)
Creatinine level, mg/100 mL	0.19 (<0.0001)	0.24 (<0.0001)	0.16 (<0.0001)
ALP level, IU/L	0.0093 (0.52)	0.039 (0.095)	−0.0039 (0.83)
Daily prednisolone dose, mg/day	−0.071 (<0.0001)	−0.057 (0.016)	−0.074 (<0.0001)
Weekly MTX dose	−0.082 (<0.0001)	−0.098 (<0.0001)	−0.072 (<0.0001)

Values are the correlation coefficient, and P value is determined using Pearson correlation coefficients. See Table 1 for definitions

[a]Eighteen patients did not have DAS28 data

Table 4 Multivariate associations of patient characteristics with the presence of vitamin D deficiency (<20 ng/mL) in Japanese patients with rheumatoid arthritis (associations examined using a forward stepwise regression model)

Characteristics	Odds ratio (95 % confidence interval)	*P* value
Female gender	2.34 (1.88–2.92)	<0.0001
Age, per 10 years	0.72 (0.68–0.77)	<0.0001
Present or past smoking	1.21 (1.02–1.42)	0.025
J-HAQ disability score	1.20 (1.07–1.36)	0.0028
DAS28	0.95 (0.87–1.04)	0.31
Patient general VAS	1.00 (1.00–1.01)	0.086
Total protein level, g/100 mL	0.81 (0.70–0.94)	0.0056
TC level, per 10 mg/100 mL	0.96 (0.94–0.98)	0.0002
ALP level, per 10 IU/L	1.01 (1.00–1.02)	0.0022
Creatinine level, mg/100 mL	0.80 (0.56–1.10)	0.17
NSAID use	1.27 (1.11–1.46)	0.0008
Biologic use	1.20 (0.98–1.49)	0.084
Daily prednisolone dose, mg/day	1.04 (1.01–1.07)	0.019

See Table 1 for definitions

women in Japanese [21]. Among Japanese patients with RA, younger patients may tend to have lower vitamin D intake than older patients.

There was an inverse relationship between 25(OH)D levels and J-HAQ disability score among all RA patients and between 25(OH)D level and DAS28 only in patients with DAS28 ≥2.6 (Table 3). Vitamin D deficiency was significantly associated with J-HAQ disability score but not DAS28 (Table 4). Several previous studies reported that HAQ disability score is significantly inversely associated with 25(OH)D levels [3, 4, 6, 10] and correlated with vitamin D deficiency [8]. Our results confirmed these reports in Japanese patients with RA. Although the inverse relationship between 25(OH)D level and DAS28 was reported previously [3, 4, 6, 7, 10], most of these previous studies used univariate analysis [3, 4, 10]. Haque et al. reported that 25(OH)D level was inversely associated with DAS28 in patients with active RA (DAS28 ≥2.6) in 62 RA patients using univariate analysis [4], and we confirmed this correlation in our larger cohort of Japanese patients with RA. Patel et al. reported that baseline levels of vitamin D were associated only with HAQ disability score at 1 year although there was an inverse relationship between 25(OH)D levels and DAS28, and between 25(OH)D levels and HAQ disability score at baseline [6]. The association between vitamin D deficiency and DAS28 was not observed in two studies [1, 5]. This finding along with our results suggests that disability rather than disease activity may be a primary determinant of serum vitamin D levels in patients with RA.

Serum total cholesterol level was positively associated with vitamin D level and negatively correlated with vitamin D deficiency in our study (Tables 1, 3, and 4). Recently, two studies reported a significant positive relationship between serum vitamin D and total cholesterol [22, 23]. We confirmed this association in Japanese patients with RA. Haque et al. reported a positive association between vitamin D level and high density lipoprotein (HDL) in patients with RA [11]. Since we did not measure serum HDL level, further studies evaluating this parameter are needed to better understand the association between cholesterol and vitamin D in Japanese patients with RA.

We found a positive association of serum ALP level with vitamin D deficiency in multivariate logistic regression analysis (Table 4) but did not find a significant correlation in unadjusted analysis of these variables (Table 3). Jesudason et al. reported an inverse correlation between serum 25(OH)D level and ALP in postmenopausal Caucasian women [24]. Adami et al. reported that patients with vitamin D deficiency tend to have higher bone ALP levels than those without deficiency [25]. Our results were consistent with these reports [24, 25] and might indicate an impairment of bone mineralization.

In our study, total serum protein was significantly inversely associated with vitamin D deficiency (Table 4). Patients with vitamin D deficiency tend to have significantly lower weight and BMI than those without deficiency (Table 1). Since serum total protein levels are considered a marker of nutritional status, our results suggest that RA patients with low total protein levels may have vitamin D-deficient diets.

In this study, NSAID use was significantly associated with vitamin D deficiency (Tables 1 and 4). NSAID users tend to have greater joint pain that may prevent them from going outside as often as non-users. They may be less likely to be active and have less exposure to sunlight compared to non-users although further studies are needed to confirm this.

Although this is the largest study evaluating vitamin D levels in RA patients, our study has some limitations. First, data on patient characteristics and medications were obtained using self-reported questionnaires; some degree of underreporting is likely. Second, our study was cross-sectional; therefore, it is not possible to determine the temporal nature of the observed associations. Third, we did not evaluate seasonal variation in vitamin D levels. Fourth, we did not collect data on vitamin D_3 dosage and vitamin D supplementation although alfacalcidol prescribed by physicians was typically used and self-supplementation is not common in Japan.

In conclusion, we evaluated the prevalence of 25(OH)D deficiency and associations with clinical characteristics in Japanese patients with RA at a single institution. Vitamin D

deficiency appears to be common in Japanese patients with RA, as previously reported for patients of other ethnicities. Female gender, younger age, high HAQ disability score, low serum levels of total protein and total cholesterol, high serum ALP levels, and NSAID use appear to be associated with vitamin D deficiency in Japanese patients with RA. Prospective studies are needed to draw stronger conclusions about risk factors for vitamin D deficiency and the association of vitamin D deficiency and fractures in Japanese patients with RA.

Acknowledgments We thank all members of the Institute of Rheumatology, Tokyo Women's Medical University for the successful management of the IORRA cohort and Drs. Tatsuhiko Kuroda, Naoko Tsugawa, and R. L. Wilder for their useful suggestions. This work was supported in part by a grant from the Japan Osteoporosis Society (Dr. Furuya). The IORRA cohort was supported by non-restricted research grants from 40 pharmaceutical companies: Abbott Japan Co., Ltd.; Asahi Kasei Kuraray Medical Co., Ltd.; Asahi Kasei Pharma Corporation; Astellas Pharma Inc.; AstraZeneca K.K.; Bristol-Myers Squibb; Chugai Pharmaceutical Co., Ltd.; Daiichi Fine Chemical Co., Ltd.; Daiichi Sankyo Co., Ltd.; Dainippon Sumitomo Pharma Co., Ltd.; Eisai Co., Ltd.; GlaxoSmithKline K.K.; Hisamitsu Pharmaceutical Co., Inc.; Janssen Pharmaceutical K.K.; Japan Tobacco Inc.; Kaken Pharmaceutical Co., Ltd.; Kissei Pharmaceutical Co., Ltd.; Kowa Pharmaceutical Co., Ltd.; Maruho Co., Ltd.; Mitsubishi Chemical Medience Corporation; Mitsubishi Tanabe Pharma Corporation; Mochida Pharmaceutical Co., Ltd.; MSD K.K.; Mundipharma K.K., Nippon Chemiphar Co., Ltd.; Nippon Shinyaku Co., Ltd.; Novartis Pharma K.K.; Otsuka Pharmaceutical Co., Ltd.; Pfizer Japan Inc.; Sanofi-Aventis K.K.; Santen Pharmaceutical Co., Ltd.; Sanwa Kagaku Kenkyusho Co., Ltd.; Sekisui Medical Co., Ltd.; Shionogi & Co., Ltd.; Taisho Toyama Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Company Limited; Teijin Pharma Limited; Torii Pharmaceutical Co., Ltd.; Toyama Chemical Co., Ltd.; UCB Japan Co., Ltd.; Wyeth K.K.; and Zeria Pharmaceutical Co., Ltd.

Conflict of interest HY has received a research grant from: Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc.; Wyeth K.K., Daiichi Sankyo Co., Ltd.; Banyu Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corporation; Abbott Japan Co., Ltd.; Eisai Co., Ltd.; Santen Pharmaceutical Co., Ltd.; Taishotoyama Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Company Limited; Kissei Pharmaceutical Co., Ltd.; and Janssen Pharmaceutical K.K. and a lecture fee and/or consulting fee from: Abbott, Eisai Co., Ltd.; Takeda Pharmaceutical Company Limited; Mitsubishi Tanabe Pharma Corporation; Janssen Pharmaceutical K.K.; Hoffmann-La Roche; and Chugai Pharmaceutical Co., Ltd. The other authors have no conflicts of interest to state.

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ASBMR 2012.9.

Effect of gamma-glutamyl carboxylase gene polymorphism on the association between serum vitamin K and gamma-carboxylation of osteocalcin in young adults

Mayu Haraikawa [1], Naoko Tsugawa [2], Natsuko Sogabe [3], Rieko Tanabe [1], Yuka Kawamura [1], Toshio Okano [2], Takayuki Hosoi [4], Masae Goseki-Sone [1]

[1] Department of Food and Nutrition, Faculty of Human Sciences and Design, Japan Women's University, Tokyo, Japan
[2] Department of Hygienic Sciences, Kobe Pharmaceutical University, Kobe, Japan
[3] Department of Health and Nutrition Sciences, Faculty of Human Health, Komazawa Women's University, Tokyo, Japan
[4] Department of Clinical Research and Development, National Center for Geriatrics and Gerontology, Aichi, Japan

Abstract:

Osteoporosis results from complex interactions between genetic and environmental factors. Nutrition is one of the most important environmental factors in the prevention of osteoporosis. Vitamin K acts as a cofactor for gamma-glutamyl carboxylase (GGCX), which is an essential enzyme for the gamma-carboxylation of vitamin K-proteins such as osteocalcin (OC). OC is produced in osteoblasts, and fully carboxylated osteocalcin binds to the calcium ion of hydroxyapatite. The amount of OC which is not carboxylated (undercaroxylated OC: ucOC) is considered a sensitive index of the vitamin K status of bone, and an elevated ratio of ucOC to intact OC is thought to be associated with low dietary intakes of vitamin K. Recent studies have demonstrated that a significantly higher association between the single

nucleotide polymorphisms of GGCX (R325Q, 974G>A) were associated bone mineral density among postmenopausal women. In this study, we aimed the effect of GGCX polymorphism on the correlation among vitamin K intake, the level of serum vitamin K, the ratio of ucOC to intact OC. Serum biochemical parameters, such as serum PK, MK-7, intact OC, ucOC, bone-type alkaline phosphatase were measured in healthy young males (n=97, age: 22.3 ± 1.7 y, mean ± standard deviation) and females (n=92, age: 21.8 ± 1.8 y). Dietary nutrient intakes were measured based on 3-day food records before the day of blood examinations. All subjects were genotyped for polymorphism (R325Q) presence. Dietary vitamin K intake from vegetables was significantly correlated with the level of serum PK, and vitamin K intake from fermented beans, natto, was also significantly correlated with the level of serum MK-7. The ratio of ucOC to intact OC showed negative association with the total vitamin K intake and serum MK-7 in both male ($r=-0.333$, $p=0.001$) and female subjects ($r=-0.549$, $p<0.001$). Interestingly, grouped by the GGCX genotype, a significant interaction between the ratio of ucOC to intact OC with serum MK-7 was observed in 325R homozygotes ($r=-0.411$, $p=0.007$, $r=-0.552$, $p<0.001$) and heterozygotes ($r=-0.358$, $p=0.015$, $r=-0.540$, $p<0.001$), but not in 325Q homozygotes in both male and female subjects. These results suggested that effect of the GGCX gene polymorphism on the correlation between the levels of serum MK-7 and gamma-carboxylation of serum OC.

Arch Osteoporos
DOI 10.1007/s11657-012-0109-9

POSITION PAPER

Japanese 2011 guidelines for prevention and treatment of osteoporosis—executive summary

Hajime Orimo · Toshitaka Nakamura · Takayuki Hosoi · Masayuki Iki · Kazuhiro Uenishi · Naoto Endo · Hiroaki Ohta · Masataka Shiraki · Toshitsugu Sugimoto · Takao Suzuki · Satoshi Soen · Yoshiki Nishizawa · Hiroshi Hagino · Masao Fukunaga · Saeko Fujiwara

Received: 7 September 2012 / Accepted: 16 October 2012

Abstract
Introduction In 1998, the first Japanese practice guidelines on osteoporosis was published. It has been updated several times, with the most recent being the full-scale 2011 edition and its abridged edition. The present guidelines provide information for the managements of primary osteoporosis in postmenopausal women and men over 50 years old, a summary of the evidence for the treatment of secondary osteoporosis, and a summary of the evidence for the prevention of osteoporosis in younger people.

A Report of the Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis: Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation

H. Orimo
Japan Osteoporosis Foundation,
Tokyo, Japan

T. Nakamura
Department of Orthopedic Surgery, School of Medicine,
University of Occupational and Environmental Health,
Kitakyushu, Fukuoka, Japan

T. Hosoi (✉)
Department of Clinical Research and Development, National Center for Geriatrics and Gerontology,
35 Gengo, Morioka-machi,
Obu City, Aichi Prefecture 474-8511, Japan
e-mail: t-hosoi@ncgg.go.jp

M. Iki
Department of Public Health,
Kinki University Faculty of Medicine,
Osakasayama, Osaka, Japan

K. Uenishi
Laboratory of Physiological Nutrition, Kagawa Nutrition University,
Sakato, Saitama, Japan

N. Endo
Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences,
Niigata, Niigata, Japan

H. Ohta
Clinical Medical Research Center,
Women's Medical Center of Sanno Medical Center,
Tokyo, Japan

M. Shiraki
Research Institute and Practice for Involutional Diseases,
Azumino, Nagano, Japan

T. Sugimoto
Internal Medicine I, Shimane University Faculty of Medicine,
Shimane, Shimane, Japan

T. Suzuki
Research Institute, National Center for Geriatrics and Gerontology,
Obu, Aichi, Japan

S. Soen
Department of Orthopaedic Surgery and Rheumatology,
Nara Hospital, Kinki University School of Medicine,
Ikoma, Nara, Japan

Y. Nishizawa
Osaka City University,
Osaka, Osaka, Japan

H. Hagino
School of Health Science, Tottori University Faculty of Medicine,
Yonago, Tottori, Japan

Published online: 01 December 2012

Method The present Executive Summary is primarily based on the content of the 2011 Japanese abridged edition. One of the key changes is revision of the criteria for initiation of pharmacological treatment, along with an introduction of the fracture risk factors used in FRAX®. Key figures and tables were selected from the Japanese abridged edition and a reference list was added.

Result and conclusions The essential points of the Japanese practice guidelines on osteoporosis were translated into English for the first time. It is hoped that the content of the guidelines becomes known throughout the world.

Keywords Criteria for initiation of pharmacological treatment · Diagnosis of osteoporosis · Fracture risk assessment · Prevention of osteoporosis · Secondary osteoporosis · Treatment of osteoporosis

Preamble

In 1998, we published the "Guidelines for (Pharmacological) Treatment of Osteoporosis 1998" under the name of the Working Group for Developing Guidelines for Osteoporosis in the Osteoporosis Research Project supported by the Ministry of Health and Welfare (present-day Ministry of Health, Labor, and Welfare) of Japan. Although they were the first Japanese guidelines for the diagnosis and treatment of osteoporosis and also set a precedent for evidence-based practice guidelines in Japan, there were few effective therapeutic agents for osteoporosis available in Japan at that time. The 1998 edition was updated in 2002.

There has been tremendous change in the field of osteoporosis inside and outside Japan since that update. Addressing osteoporosis has become a more urgent issue also in Japan because of its fast-aging society. Therefore, we published the comprehensive "Guidelines for Prevention and Treatment of Osteoporosis 2006" under the name of the Committee for Developing Guidelines for Prevention and Treatment of Osteoporosis 2006, an ad hoc organization comprising the Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation. Emphasizing prevention, covering secondary osteoporosis, presenting the criteria for initiation of pharmacological treatment, and grading the recommendation for each therapeutic agent, these guidelines were highly rated in the medical and clinical arenas. Immediately thereafter we published an abridged edition to disseminate the content of the 2006 Guidelines to a greater number of doctors and healthcare professionals.

In late 2011, the 2006 Guidelines and its abridged edition were updated. Key changes are as follows: profile of the research progress on bone quality, revision of the criteria for initiation of pharmacological treatment (associated with the re-examination of the risk factors for fracture and introducing FRAX®), more detailed descriptions about secondary osteoporosis (including new information on the relationship between lifestyle-related diseases and fracture risk), evaluation of new therapeutic agents, and bone metabolic markers covered by public insurance. The present Executive Summary is primarily based on the content of the updated 2011 Japanese abridged edition. Only the most key figures and tables were selected from the Japanese abridged edition and a reference list was added. We hope this Executive Summary contributes to the advancement of medical care for osteoporosis in Asia and the world.

In developing the guidelines, a systematic literature search of MEDLINE, EMBSE, Cochrane Library, and PubMed was conducted. The treatment recommendations in these clinical guidelines were determined by the consensus of the committee. The draft guidelines were available for physician comments at the annual meetings of the Japan Osteoporosis Society in 2010 and 2011.

The funding for all costs to produce the guidelines and this position paper was obtained from the Japan Osteoporosis Society, Japanese Society for Bone and Mineral Research, and Japan Osteoporosis Foundation. All of the authors state they have no conflict of interest related to the guidelines or this position paper.

Definition, epidemiology, and etiology

Definition

The United States National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy held in 2000 proposed a new definition of osteoporosis as follows: Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fractures. Further, it was stated that bone strength reflects the integration of two main features: bone mineral density (BMD), which accounts for almost 70 % of bone strength, and bone quality, which accounts for the remaining 30 %.

Risk factors for fractures vary among individuals, and include presence or absence of fragility fractures, family history, lifestyle factors, as well as BMD. Therefore, in clinical practice, the risk of fracture should be comprehensively evaluated based on these clinical risk factors for each individual.

M. Fukunaga
Kawasaki Medical School,
Kurashiki, Okayama, Japan

S. Fujiwara
Department of Clinical Studies, Radiation Effects Research Foundation,
Hiroshima, Hiroshima, Japan

Recently, some algorithms have been developed to quantitatively estimate an individual's fracture risk by integrating multiple risk factors (see "Risk factors for fracture" for FRAX®).

Epidemiology

The estimated number of osteoporotic patients aged 40 or over in Japan is 12,800,000 (3,000,000 men and 9,800,000 women), based on the result of a survey of the prevalence of osteoporosis (diagnosed with BMD at the lumbar vertebrae or proximal femur) stratified by age in the general population (Fig. 1) [1] and the population structure stratified by age groups in 2005. Furthermore, the estimated annual incidence of osteoporosis, based on the BMD at the lumbar vertebrae in the population aged between 40 and 79 years, is 0.6 % in men and 2.3 % in women.

The estimated incidence of proximal femoral fractures due to osteoporosis in Japan was 148,100 (31,300 men and 116,800 women) in 2007 [2]. A follow-up study targeting a rural population revealed that the 10-year cumulative incidence of vertebral fractures was 5.1 and 14 % for men and women in their 60s, respectively, and 10.8 and 22.2 % among men and women in their 70s, respectively [3]. However, a long-term trend shows that a later year of birth is associated with a lower incidence of vertebral fractures.

The incidence of proximal femoral fractures was found to be higher in western Japan than in eastern Japan. As compared to reports from Western countries, the incidence of proximal femoral fractures is lower and that of vertebral fractures is similar or higher in Japan.

Etiology

From middle-age onward, BMD decreases and bone quality deteriorates with advancing age, resulting in loss of bone strength. Especially in women, BMD decreases sharply in the perimenopausal period and for several years thereafter. In addition to this natural course, genetic factors, nutritional deficiency since childhood and puberty, lack of exercise, and unhealthy lifestyle also cause loss of bone strength. Primary osteoporosis is the clinical condition in which these factors have caused a significant loss of bone strength.

Bone remodeling consists of bone resorption by osteoclasts and bone formation by osteoblasts, a mechanism to maintain bone strength. If bone resorption increases with advancing age and menopause and exceeds the rate of bone formation, BMD will begin to decrease. Low BMD is caused by activation of osteoclasts due to estrogen deficiency associated with menopause, and by inadequate secondary mineralization, microarchitecture deterioration, and a decrease in capacity for absorbing calcium associated with advancing age, among other factors (Fig. 2).

Inadequate secondary mineralization and microarchitecture deterioration result in deterioration of bone quality, which is, however, also affected by the cell function of synthesizing bone matrix, conditions surrounding bone matrix (i.e., levels of oxidation and glycation), and levels of vitamins D and K. When oxidative stress and glycation increase in association with aging and lifestyle-related diseases, the non-enzymatic (nonphysiological) cross-links (see "Prevention of falls") increase between collagen molecules in the bone matrix, resulting in a loss of bone strength (Fig. 2).

Prognosis

Fractures associated with osteoporosis, in particular proximal femoral fractures, lead to impairment in mobility and vital functions and an increase in mortality. The relative risk of overall mortality is high in older women with a low BMD and vertebral deformity, and the greater the number of vertebral fractures, the higher the risk of mortality. Decreased BMD at the proximal femur increases the long-

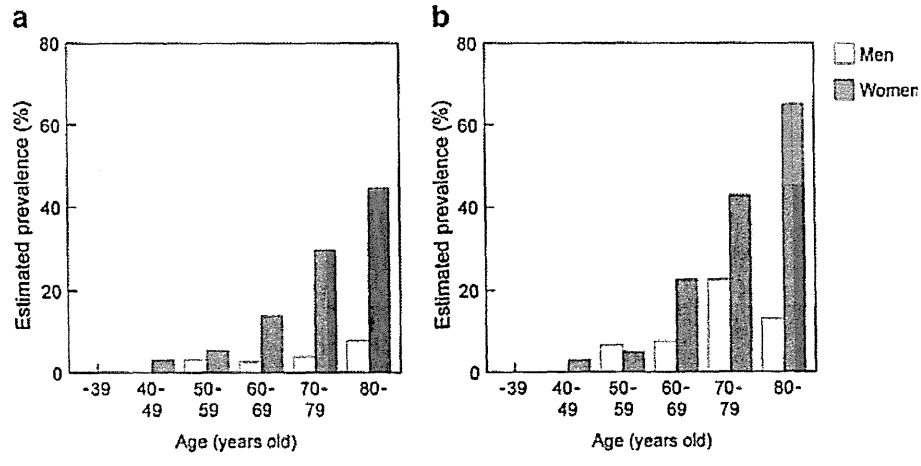

Fig. 1 Estimated prevalence of osteoporosis in Japan. Osteoporosis was diagnosed from BMD at vertebrae L_{2-4} (a) and proximal femur (b). Data from Yoshimura [1] (Copyright© 2009 Springer Science + Business Media BV)

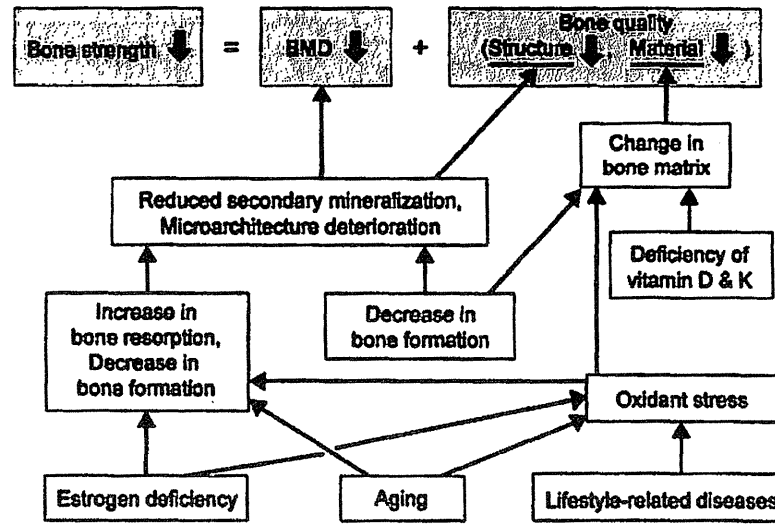

Fig. 2 Factors causing deterioration of bone strength

term mortality risk, regardless of the presence or absence of vertebral fracture.

According to a survey on quality of life (QOL), patients with osteoporosis score lower on factors related to posture/body shape and falls/psychological in a self-assessment of QOL than persons in the general population who have undergone an osteoporosis screening.

Low BMD is strongly related to the Certification of Needed Long-Term Care for the public nursing-care insurance system in Japan. That is, osteoporosis or low BMD is one of the most significant factors for becoming fragile/immobilized or even becoming bedridden or institutionalized. Therefore, prevention of osteoporotic fractures is likely to prevent reduced mobility or immobilization.

Diagnosis

Diagnostic procedures

The procedures for diagnosis of osteoporosis are shown in Fig. 3 [4].

For the diagnosis of osteoporosis, a medical interview, physical examination, diagnostic imaging, and blood and urine examinations (including measurement of bone metabolic markers) should be conducted first. Then, bone assessment must be conducted with bone mass measurement and spinal radiography. Based on this information, diseases causing low bone mass or secondary osteoporosis should be excluded, and then an accurate diagnosis of primary osteoporosis should be made based on the diagnostic criteria (see "Diagnostic criteria for primary osteoporosis").

Information obtained in the diagnostic process about factors that could contribute to osteoporosis and the risk factors for fractures (e.g., family history, prevalent fractures, and bone metabolic markers) should be used to evaluate the severity of osteoporosis and the fracture risk. This information will also be useful to provide guidance about lifestyle modification and to select the optimal therapeutic strategy.

Clinical presentation

In the absence of a fracture, osteoporosis is nearly asymptomatic. However, patients with osteoporosis are predisposed to the development of fractures due to loss of bone strength, and the occurrence of fractures will severely impair their QOL (Fig. 4). Osteoporotic fracture is also called fragility fracture.

Proximal femoral fractures directly lead to decreases in the activities of daily living (ADL) and can lead to patients being bedridden, resulting in poor prognosis.

The estimated prevalence of vertebral fractures in Japanese in their early 70s is 25 % and is 43 % in person over 80 years old. The occurrence of vertebral fractures often leads to subsequent vertebral fractures. Since a vertebral deformity persists after the fracture heals, accumulation of vertebral fractures in multiple sites causes kyphosis (round back). Progressive kyphosis leads to deterioration of QOL due to significantly limited ADL and lumbar backache, and can cause functional declines or disorders of the digestive, respiratory, and cardiac systems.

Some lifestyle-related diseases which cause atherosclerosis such as diabetes mellitus (DM), hypertension, dyslipidemia, and chronic kidney diseases (CKD) have attracted attention in relation to osteoporosis. In particular, DM and CKD predispose patients to osteoporosis, and increase their fracture risk (see "Prevention of falls"). The possibility of hidden osteoporosis always should be considered during medical care of patients with lifestyle-related diseases.

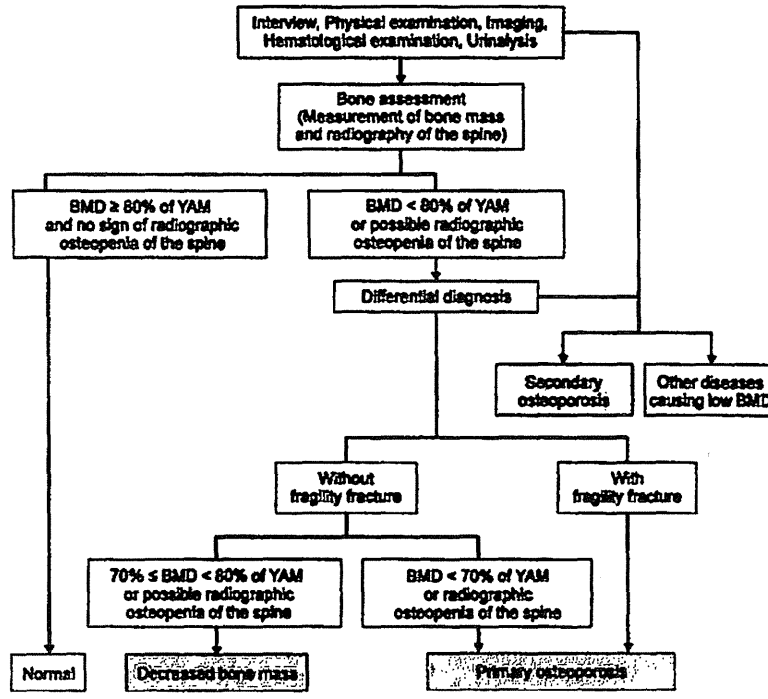

Fig. 3 Procedure for the diagnosis of osteoporosis. *YAM* young adult mean (20 to 44 years of age). Adapted from Orimo [4] (Copyright© 2001 Springer Science + Business Media BV)

Medical interview and physical examination

The objectives of the medical interview and physical examination are to assess the presence and symptoms of osteoporotic fractures, risk factors for osteoporosis and fractures, and to obtain information for the differential diagnosis.

Family history of proximal femoral fractures (in either or both parents), loss of height (4 cm or more relative to the height at 25 years of age), current smoking, and excessive alcohol consumption (3 units/day or more, 1 unit=8–10 g ethanol) are particularly important risk factors for osteoporotic fractures. Therefore, taking a careful history including these factors is needed. History of glucocorticoids use, rheumatoid arthritis, and lifestyle-related diseases such as diabetes mellitus are important information for the differential diagnosis.

In regard to the physical findings, a rounded back, fewer than 20 teeth, and a value of less than −4 on the Female Osteoporosis Self-Assessment Tool for Asians are key factors that strongly suggest osteoporosis.

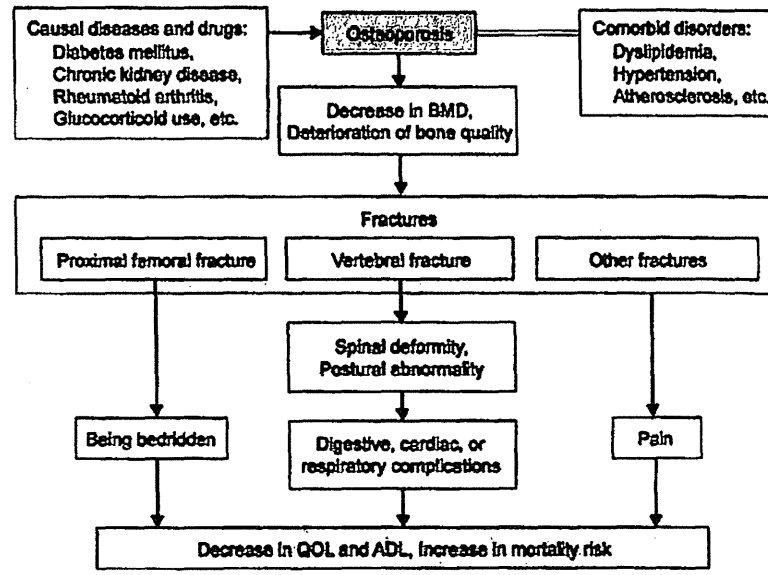

Fig. 4 Clinical presentation and prognosis of osteoporosis

Bone assessment

It is recommended that BMDs of the lumbar spine and/or proximal femur are measured by dual-energy X-ray absorptiometry (DXA). When there is a fracture or deformity in the lumbar vertebrae that increases the influence of an artifact on spine BMD, the data of lumbar spine should not be used. If the measurement at either of these sites is not successful (because of bilateral hip surgery, multiple fractures of the lumbar vertebra, severe vertebral deformity, or excessive obesity, etc.), another choice is forearm bone.

Microdensitometry has been developed in Japan to radiologically assess BMD, mainly of cortical bone in the second metacarpal.

The speed of sound and broadband ultrasound attenuation through bone are measured with quantitative ultrasound (QUS). This is a non-invasive measurement technique and may provide reliable information on bone quality along with the BMD. However, it is easily affected by measurement conditions, among other factors. The parameters used in QUS were standardized by the QUS Standardization Committee of the Japan Osteoporosis Society in 2010 [5].

Fracture evaluation

Radiography of the thoracic and lumbar vertebrae are essential for assessment of fracture, deformity, or change in the vertebrae, and for exclusion of other similar disorders that present with lower back pain, round back, or low bone mass. In the Japanese diagnostic criteria, the presence of fragility fractures alone confirms the diagnosis of osteoporosis (see "Diagnostic criteria for primary osteoporosis"). Since most of the prevalent fragility fractures, however, are vertebral fractures, usually without pain, radiography is fundamental for their proper diagnosis. Either semiquantitative assessment or quantitative morphometry is used. The lateral DXA images for vertebral fracture assessment can be used, but more clinical experience in Japan is needed to make a recommendation.

If used during the early period after a fracture has occurred (within 2 weeks), MRI provides a better diagnostic yield than plain radiography. MRI is helpful particularly for fresh vertebral fractures, because the height of the vertebral body often does not decrease in the early period. Since it is, however, impractical to diagnose all the cases with MRI, MRI is recommended when it is necessary to distinguish osteoporotic fractures including non-vertebral fractures from those caused by other diseases, or for a detailed examination regarding complicating diseases.

Bone metabolic markers

The increase of bone metabolic markers is a BMD-independent predictor of fractures, and bone metabolic markers are one of the indices of fracture risk. There are two types of bone metabolic markers: bone resorption markers and bone formation markers. Examinations of blood or urine for these bone metabolic markers easily provide information on the bone metabolic state (Fig. 5) [6].

Bone metabolic markers are useful particularly for the following situations. (1) The patient has little understanding of the need for treatment. (2) The patient is scheduled to receive pharmacotherapy. (3) It is difficult to decide what drug to choose. (4) You want to adopt an appropriate treatment for the patient's pathological condition. Bone metabolic markers are also useful for evaluation of the response to treatment. Thus, it is recommended to measure them at the time of diagnosis if possible.

Among bone metabolic markers, undercarboxylated osteocalcin (ucOC) can be used as an index of vitamin K deficiency in the bones.

When the values of bone resorption markers are abnormally high, the presence of other metabolic bone diseases is suspected.

Differential diagnosis

The targets of differentiation from primary osteoporosis are secondary osteoporosis and other bone-related diseases. Secondary osteoporosis is caused by other diseases or treatments, but its clinical state can seem similar to that of primary osteoporosis, while other bone-related diseases display a clinical state that is different from that of primary osteoporosis. Some instances of secondary osteoporosis and other bone-related diseases are critical or require immediate medical attention. Further, most types of secondary osteoporosis require a therapeutic strategy different from that for primary osteoporosis, and the appropriate treatment of the causative diseases may lead to a dramatic improvement in secondary osteoporosis. Therefore, the differential diagnosis is an extremely important process, despite the prevalence of secondary osteoporosis being low. The probability of secondary osteoporosis is relatively high among premenopausal women and men.

Information for the differential diagnosis can be obtained in every step of the diagnostic process. In the medical interview, thorough medical and surgical histories are needed, including current medications. Radiography may be useful for exclusion of osteomalacia and bone metastases of malignant tumors. Various causative states of secondary osteoporosis may be suspected by the results of blood and urine examinations, for example, hypercalcemia, hypocalcemia, elevated alkaline phosphatase level, and proteinuria.

It is usually considered that patients who visit specialized medical institutes, such as university hospitals, are likely to have secondary osteoporosis due to endocrine diseases and others.

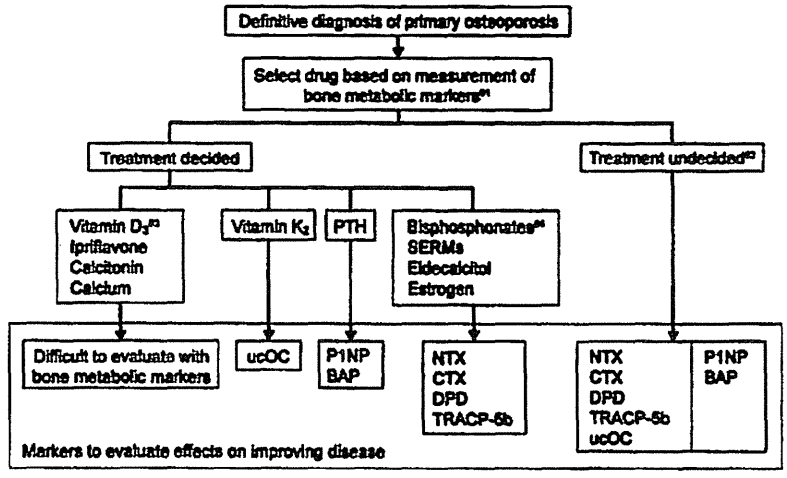

Fig. 5 Measurement of bone metabolic markers in drug treatment of osteoporosis. #1: in patients taking bisphosphonates, measure after stopping drug for at least 6 months, and in patients taking other osteoporosis drugs, measure after stopping drug for at least 1 month. #2: measure one type each of a resorption marker and formation marker. #3: excluding eldecalcitol. #4: in patients expected to be on long-term bisphosphonate therapy, measure bone resorption markers and BAP or P1NP. Nishizawa [6] (Copyright© 2012 Springer Science + Business Media BV)

Diagnostic criteria for primary osteoporosis

After excluding both the presence of other diseases characterized by low bone mass and the possibility of secondary osteoporosis, primary osteoporosis should be diagnosed by a two-step approach: (1) presence or absence of fragility fractures and (2) BMD or assessment of osteopenia on spinal radiography (Fig. 6) [4].

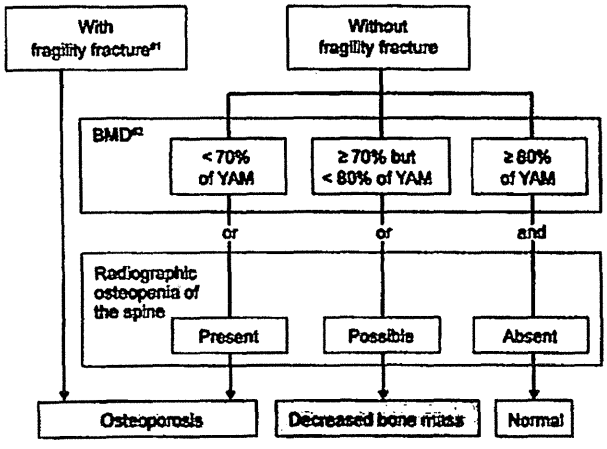

Fig. 6 Diagnostic criteria for primary osteoporosis (updated in 2000). Primary osteoporosis is diagnosed according to these criteria in the absence of diseases causing low bone mass or secondary osteoporosis. #1: fragility fracture is a nontraumatic bone fracture that is caused by slight external force to a bone with low BMD (BMD less then 80 % of YAM). Sites of fracture include the spine, proximal femur, and the distal end of the radius. #2: BMD usually refers to lumbar BMD. However, when the measurement is inappropriate for reasons such as spinal deformity, the proximal femur BMD should be used. When measurement at those sites is difficult, BMD of the radius, second metacarpal bone, or calcaneus will be used. Revision of additional T-scores is under consideration. Adapted from Orimo [4] (Copyright © 2001 Springer Science + Business Media BV)

Primary osteoporosis is diagnosed on the presence of any fragility fractures (defined as a nontraumatic bone fracture caused by slight external force to a bone with low bone mass, which correlates to a BMD<80 % of young adult mean (YAM) or radiographic osteopenia of the spine) at sites including spine, proximal femur, and the distal end of radius. If there is no fragility fracture, the BMD level is used to diagnose the patient as "normal", "decreased bone mass", or "osteoporosis". Evaluation of osteopenia based on spinal radiography should be used as supplementary means, and quantitative bone densitometry is preferable for bone assessment.

The T-score to YAM of BMD, not the percentage, is used as diagnostic criteria internationally. A T-score of −1.5 represents a value of −1.5 standard deviation of the YAM and is approximately equivalent to 80 % of the YAM in Japan. A T-score of −2.5 is approximately equivalent to 70 % of the YAM. Internationally, the proximal femur is considered to be the standard measurement site for BMD.

Risk factors

Risk factors for fracture

Major risk factors for osteoporotic fractures are female gender, advanced age, low BMD, and prevalent fractures. In addition, many other factors affect fracture risk directly or indirectly. Although a poor intake of calcium increases fracture risk via low BMD, other risk factors for fractures such as age, prevalent fracture, family history of fractures, smoking, and drinking are independent of BMD. Low body weight also is a BMD-independent risk factor, but only for proximal femoral fractures.

The FRAX® (Fracture Risk Assessment Tool) was developed to estimate the 10-year probability of fractures in individual patients by the World Health Organization (WHO) in 2008 based on 11 risk factors identified from worldwide data in ten cohorts. FRAX is a convenient tool to easily identify a person at high risk for fractures, and therefore has been incorporated into the criteria for initiation of pharmacological treatment in the present guidelines (see "Criteria for initiation of pharmacological treatment").

Prevention

Primary prevention of osteoporosis

The most important measure for primary prevention of osteoporosis is education appropriate to each age group: in early life to acquire as high a peak bone mass (PBM) as possible, to maintain acquired PBM through exercise thereafter, and to minimize its decrease after menopause.

A study on the age-specific distribution of bone mass in Japanese women revealed that PBM is achieved at 18 years of age [7]. Thus, before age 18 is the most effective time for physicians to encourage young people to increase PBM to its maximal level. Guidance on maintenance of adequate weight, active intake of calcium, and weight-bearing exercise is effective.

For middle-aged and older persons, guidance on maintenance of adequate weight, aerobic exercises especially walking, and weight-bearing exercise is effective. Smoking cessation and limiting alcohol intake to less than 3 units/day (1 unit=8–10 g ethanol) is likely to decrease the fracture risk.

Prevention of falls

Most proximal femoral fractures in elderly people occur because of a fall. Risk factors for proximal femoral fractures are a past history of falls and the number of falls, and fall-related factors including generalized weakness, paralysis, muscular weakness, use of sleep-inducing drugs, and decreased vision.

Approaches to prevent falls include (1) exercise interventions (e.g., training to increase strength of muscle, balance, walking ability, and flexibility); (2) non-exercise interventions (e.g., instruction about medication, diet, and environment, along with education and guidance for behavior modification); and (3) multifactorial intervention (e.g., in addition to 1 and 2, an individualized approach based on the physical and mental functioning, environment, and medical assessment of a patient).

In elderly people, vitamin D deficiency increases the risk of falls, and administration of vitamin D can reduce the frequency of falls.

Wearing a hip protector is effective for the prevention of proximal femoral fractures; especially in high-risk groups in elderly care facilities.

Osteoporosis screening

Osteoporosis screening is spreading as a part of the Elderly Health Services (currently as a project under the Health Promotion Law) in Japan, and is performed every 5 years in women from 40 to 70 years old. The screening rate (the percentage of women who underwent osteoporosis screening against the entire target female population) was 4.6 % in 2005.

Osteoporosis screening for people of middle and older age is aimed at early detection of asymptomatic osteoporotic patients and persons at risk of osteoporosis to prevent future fractures. Persons at risk of osteoporosis should be given guidance on diet and exercises, and asymptomatic patients should be targets for early intervention (secondary prevention).

In screening, persons should be classified as either "Complete examination required", "Guidance required", or "No apparent abnormality" based on the results of the medical interview and bone mass measurement (Fig. 7) [8]. The criteria for requiring a complete examination is a bone mass of less than 80 % of YAM; this is different from the diagnostic criteria for osteoporosis (i.e., when BMD is less than 70 % of YAM in the absence of fragility fracture). In addition, bone mass measurement at the calcaneus (including QUS), which is not used to diagnose osteoporosis, is also permitted in the screening. The reason for these differences is that screening should identify the persons requiring the full diagnostic assessment for osteoporosis.

FRAX® will become suitable for osteoporosis screening after the cutoff values for fracture probability are established for complete examination and for guidance.

Treatment

Criteria for initiation of pharmacological treatment

The goals of osteoporosis treatment are prevention of fracture as a complication and maintenance of good skeletal health. Important strategies to reduce the fracture risk in osteoporotic patients are treatment with a bone resorption inhibitor or bone formation stimulant and guidance to establish a lifestyle that leads to maintenance and enhancement of bone strength and to avoid risk factors for fractures, such as a fall, that are independent of a decrease in bone strength.

The risk factors for fracture include low BMD, factors that contribute to a decrease in BMD, and deterioration of bone matrix, including lifestyle-related diseases. A prevalent fragility fracture is the most important among all these

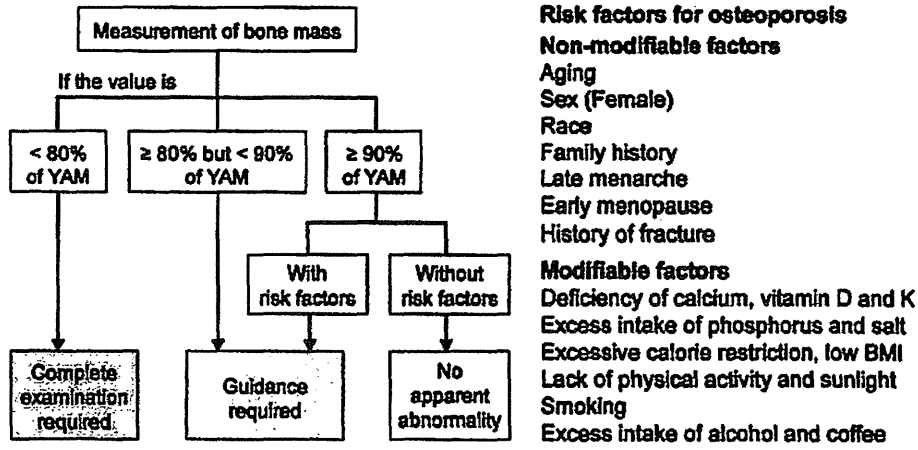

Fig. 7 Criteria for osteoporosis screening. Risk factors for osteoporosis: non-modifiable factors: aging, sex (female), race, family history, late menarche, early menopause, and history of fracture. Modifiable factors: deficiency of calcium, vitamin D, and K; excess intake of phosphorus and salt; excessive calorie restriction; low BMI; lack of physical activity and sunlight; smoking; and excess intake of alcohol and coffee Orimo [8]

factors with the exception of low BMD. Family history of proximal femoral fractures significantly increases the fracture risk even in persons without a fragility fracture who have a "low bone mass" based on their BMD.

Based on this new knowledge about risk factors and the consideration about using FRAX® (see "Risk factors for fracture"), the criteria for initiating pharmacological treatment to prevent fragility fracture was established as shown in Fig. 8. In these criteria, FRAX® is used to consider whether or not to initiate pharmacological treatment in persons without a fragility fracture who have a low bone mass. This is because persons with a fracture risk comparable to patients with osteoporosis possibly could be included in this group and need other measures to assess the magnitude of the fracture risk other than low BMD. Considering that the 10-year probability of major osteoporotic fractures in the patients receiving pharmacological treatment was observed around 15 % in Japanese clinical settings, we adopted 15 % as a treatment threshold for the persons with low bone mass. In the guidelines, FRAX® is not used in the first-line screening to determine the persons who need further examination such as bone densitometry. As stated earlier, the

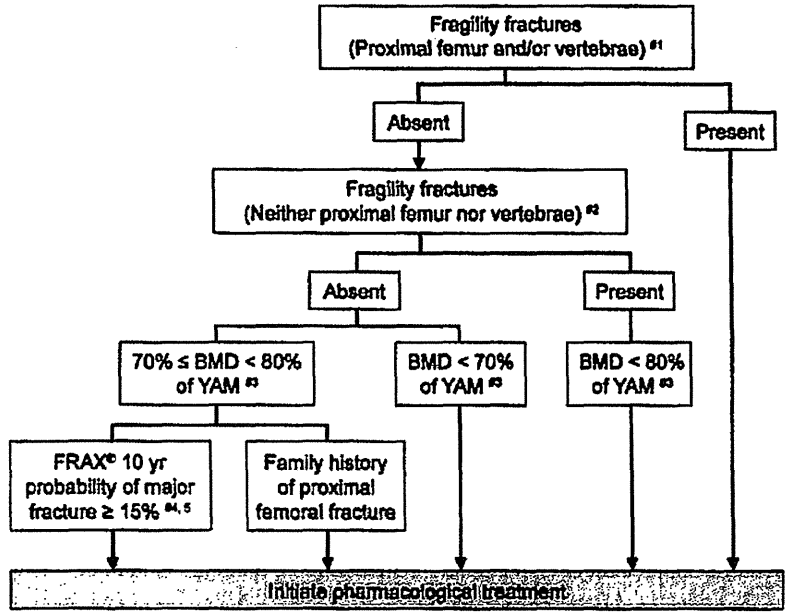

Fig. 8 Criteria for initiation of pharmacological treatment. #1: this means proximal femoral fracture and/or vertebral fracture caused by slight external force after menopause in women and after age 50 in men. #2: this means distal forearm, proximal humerus, pelvis, lower leg and/or rib fracture caused by slight external force after menopause in women and after age 50 in men. #3: revision of additional T-scores is under consideration for some measurement sites. #4: this should be applied in persons <75 years. Additionally, a lower cutoff value does not include all young persons in and around their 50s for whom pharmacological treatment is recommended based on the present diagnostic criteria. #5: as these criteria refer to primary osteoporosis, they should not be applied to persons whose FRAX® risk factors are "glucocorticoid", "rheumatoid arthritis", or "secondary osteoporosis". That is, these criteria should be applied only in persons who answer "No" to each of these items