

上記の診断基準にくわえて、他の骨折危険因子を考慮することが勧められている。

4. 薬物治療の開始基準

骨粗鬆症の薬物治療は骨折予防を目的として行われる。原則的に骨粗鬆症の診断が下った場合は薬物治療の対象となるが、この診断が下った場合と同等またはそれ以上の骨折リスクを有する場合にも薬物治療を行うことが提案されている。四肢の骨折において転倒が大きな関与をしていることはこれまで述べてきたとおりであるが、臨床的には、すでに脆弱性骨折を有していることが重要な骨折リスクである。

脆弱性骨折の部位を問わない場合、それらを有する場合の新規骨折の相対リスクは2倍程度である。一方、椎体骨折がすでに存在する場合の新規椎体骨折の相対リスクは骨量測定値による補正をした上でも3~4倍程

度、大腿骨近位部骨折の相対リスクは3~5倍程度となり、骨折部位を問わない場合に比べてリスクの上昇が大きい。脆弱性骨折が大腿骨近位部骨折の場合でも同様なリスクの上昇が認められる。

これらのことから、閉経後女性および50歳以降の男性においていずれも50歳以降に大腿骨近位部または椎体に脆弱性骨折があった場合には骨量測定の結果を問わず薬物治療を検討することが2011年版ガイドラインでは提案された³⁾。一方、大腿骨近位部骨折および椎体骨折以外の脆弱性骨折（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）があった場合には、そのことのみでの判断ではなく、骨量がYAMの80%未満である時に薬物治療を検討することになった。

既存骨折をもたない骨量減少者については、大腿骨近位部骨折の家族歴を有する場合には薬物治療を検討することとし、過度の飲酒や現在の喫煙について検討する

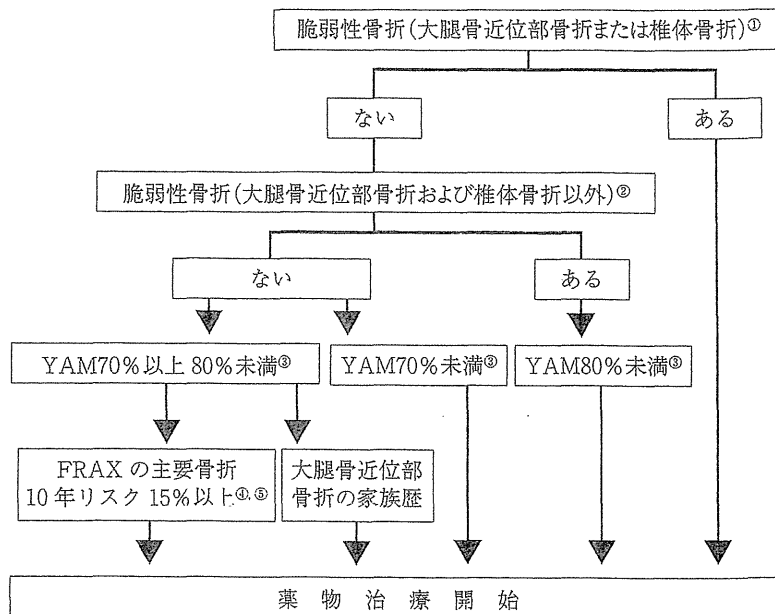


図1 原発性骨粗鬆症の薬物療法開始基準

- ①脆弱性骨折（大腿骨近位部骨折または椎体骨折）とは、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脆弱性骨折（大腿骨近位部骨折および椎体骨折以外）とは、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スコア表記の併記が検討されている。
- ④75歳未満で適用する。また、50歳台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の項目のうち関節リウマチ、糖質ステロイド、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、これらの項目はすべて「なし」である症例に限って適用される。

場合はそれらおよび他の危険因子との重なり合いを踏まえた総合的な評価はFRAX (r) ^{4,5)} を用いて行うことが提案された。日本骨粗鬆症学会を中心とする検討の結果、骨量減少者における薬物治療のカットオフ値として主要骨粗鬆症性骨折確率15%を採用することが提案された。一方、75歳以上においては、ほとんどすべての女性がこのカットオフ値を上回ることから、カットオフ値の適応は75歳未満とすることが提案された。また、50歳台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。

なお、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の項目のうち関節リウマチ、糖質ステロイド、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、これらの項目はすべて「なし」である症例に限って適用される(図1)。

5. 骨粗鬆症の治療

骨粗鬆症性脆弱性骨折のリスクを総合的に減ずることが骨粗鬆症の予防と治療における具体的な目標となる。つまり、骨折予防のためには骨のみならず、筋力の増強、関節可動域の確保といった運動能力の維持・増進や転倒防止を念頭においた環境の整備が重要であり、とくに高齢者では強調されるべきである。また、高齢者の骨粗鬆症においては骨折が発症する例も多く、その治療とケアも重要な課題であることはいうまでもない。

骨粗鬆症の治療は骨折予防を目的とし、骨脆弱性の改善を目標とする。しかしながら、骨折予防のためには骨自体の強度のみならず、筋力の増強、関節可動域の確保といった運動能力の維持・増進とともに、転倒防止を念頭においた環境の整備が重要なポイントである。

現在多くの薬剤が使用可能であり、それぞれの特徴を生かした使用が望まれる。骨粗鬆症の予防と治療ガイドラン2011年版³⁾では、それぞれの薬剤について、骨量増加効果、椎体骨折予防効果、非椎体骨折予防効果、大腿骨近位部骨折予防効果についてエビデンスが整理され、推奨グレードが提案されている。

ビタミンD関連薬であるアルファカルシドールやロカルトロールはわが国で汎用されてきたが、最近ではエル

デカルシドールが加わった。ビタミンD関連薬には骨に対する作用の他にもおそらく筋肉等にも作用し、転倒抑制効果を発揮する可能性もある。ビタミンK₂製剤(商品名グラケイ)についても骨折発生抑制効果が報告されているが、より高齢者での有用性が示唆されている。ワルファリン服用中の患者には絶対禁忌である。

ビスホスホネート薬は強力な骨吸収抑制能をもち、現在数種類のもものが使用されている。エチドロネートは、第一世代のものといわれ、間欠服用法が用いられているが、窒素含有型ビスホスホネートに比べると骨折抑制効果は弱いと言える。窒素含有ビスホスホネート薬であるアレンドロン酸、リセドロン酸、ミノドロン酸は骨折発生抑制効果の点から主要な薬剤群になっている。ビスホスホネート薬は朝食の30分以上前の空腹時にコップ一杯の水で服用することが必要である。現在は、前2者については毎日1回服用するものと週に1回服用するものがあるが、ミノドロン酸については4週に一度服用するものが市販されている。さらにアレンドロン酸については4週に1度点滴静注射するものも実用化された。

選択的エストロゲン受容体モジュレーター(selective estrogen receptor modulator, SERM)としては、ラロキシフェンとバゼドキシフェンがある。これらも骨吸収抑制作用を主な作用機序とするが男性には適用がない。閉経後骨粗鬆症患者において、骨密度増加効果と脊椎椎体骨折発生抑制効果に関するエビデンスがあり、非椎体骨折発生抑制についても報告がある。

テリパラチドは副甲状腺ホルモンの構造の一部を用いて作られたものであり、骨形成を促進させる効果をもつ。現在は骨折リスクが高い骨粗鬆症患者について用いることができる。毎日1回自己注射するものと週に1回医療機関で注射するものがある。

女性ホルモン製剤の骨代謝領域におけるこれまでのエビデンスは抱合型エストロゲン製剤によって得られたものであり、本剤は骨粗鬆症に対する保険適用をわが国においては得ていない。これらのことから、上記ガイドラインでは、女性ホルモン製剤が骨量増加効果と骨折発生抑制効果の両者を有していることに触れられているが、現在骨粗鬆症に対して保険適用を受けていないことも明記されている。

骨粗鬆症治療における最大の目的は脆弱性骨折の予防であるが、高齢者の骨粗鬆症診療においては、すでに

骨折を発生していることも多く、骨折に対する処置が必要とされることが頻発する。脊椎圧迫骨折による脊柱の変形や腰背痛はその例である。腰背痛はさまざまな疾患によって引き起こされるため鑑別診断が欠かせない。骨粗鬆症による圧迫骨折が原因である場合は、安静や湿布による局所療法他に、カルシトニン製剤による治療(筋注)が有用である。

6. おわりに

骨粗鬆症の診療には内科、整形外科、婦人科、予防医学などさまざまな領域の医師が学際的に協力することが有用である。骨折予防を念頭においた薬物療法の活用が望まれるとともに、骨折発生後の再発予防や日常活動度の維持・向上にも留意すべきである。

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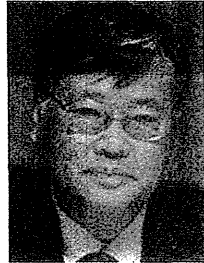
◆ 第14回日本骨粗鬆症学会シンポジウム REPORT ◆

診断基準の改訂に向けて—骨粗鬆症診療の新たな展開をめざして

2012年9月29日(土)・新潟



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●プログラム

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 2. 内科の視点から……………杉本利嗣 (島根大学医学部内科学講座内科学第一)
 3. 放射線科の視点から……………曾根照喜 (川崎医科大学放射線医学(核医学))
 4. 予防と治療のガイドラインの視点から……………細井孝之 (独立行政法人国立長寿医療研究センター臨床研究推進部)
- 総合討論

第14回日本骨粗鬆症学会(新潟)最終日の午後、今学会のハイライトの一つである原発性骨粗鬆症の診断基準改訂をめぐるシンポジウムが開かれた。骨粗鬆症診療をめぐるのは、昨年末の「骨粗鬆症の予防と治療ガイドライン2011年版」に続いて、今年初めには「骨粗鬆症診療における骨代謝マーカーの適正使用ガイドライン2012年版」が発表されている。こうしたガイドライン改訂の流れを受け、骨粗鬆症の臨床研究・診療のさらなる充実を期して、2000年以来12年ぶりに原発性骨粗鬆症の診断基準が改訂されることになった。シンポジウムでは改訂の概要と意義が各診療科の視点から解説され、総合討論では新たな基準の活用に向けてさまざまな意見が寄せられた。

診断基準改訂の経緯と概要

近年の臨床研究における新たな知見の集積を背景として、骨粗鬆症診断の国際的整合性を目指して、2011年7月に日本骨代謝学会と日本骨粗鬆症学会合同による原発性骨粗鬆症の診断基準改訂検討委員会が設立された。4回にわたる委員会での議論を受けて改訂案が作成され、さらに両学会の評議員から募ったさまざまな意見を検討してまとめられた最終案が、第14回日本骨粗鬆症学会最終日のシンポジウムの冒頭に、座長の宗圓聰氏から提示された(表1)。

委員会で議論された問題点は、わが国の基準と国際基準との違い、骨密度測定部位とカットオフ値の扱いの2点に集約されるが、宗圓氏はこの問題点に沿って改訂のポイントを解説し(表2)、改訂版診断基準では本文で改訂の背景を解説する

日本骨代謝学会、日本骨粗鬆症学会合同 原発性骨粗鬆症の診断基準改訂検討委員会

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第 14 回日本骨粗鬆症学会シンポジウム REPORT

表 1 原発性骨粗鬆症の診断基準 (改訂案)

低骨量をきたす骨粗鬆症以外の疾患または続発性骨粗鬆症を認めず、骨評価の結果が下記の条件を満たす場合、原発性骨粗鬆症と診断する。

I 脆弱性骨折^(注1)あり

1. 椎体^(注2)または大腿骨近位部骨折あり
2. その他の脆弱性骨折^(注3)があり、骨密度^(注4)がYAMの80%未満

II 脆弱性骨折なし

骨密度^(注4)がYAMの70%または $-2.5SD$ 以下

注1 軽微な外力によって発生した非外傷性骨折。軽微な外力とは、立った姿勢からの転倒か、それ以下の外力をさす。

注2 形態椎体骨折のうち、3分の2は無症候性であることに留意するとともに、鑑別診断の観点からも脊椎エックス線像を確認することが望ましい。

注3 その他の脆弱性骨折：軽微な外力によって発生した非外傷性骨折で、骨折部位は肋骨、骨盤（恥骨、坐骨、仙骨を含む）、上腕骨近位部、橈骨遠位端、下腿骨。

注4 骨密度は原則として腰椎または大腿骨近位部骨密度とする。また、複数部位で測定した場合にはより低い値を採用することとする。腰椎においてはL1~L4またはL2~L4を基準値とする。ただし、高齢者において、脊椎変形などのために腰椎骨密度の測定が困難な場合には大腿骨近位部骨密度とする。大腿骨近位部骨密度には頸部またはtotal hip (total proximal femur)を用いる。これらの測定が困難な場合は橈骨、第二中手骨の骨密度とするが、この場合は%のみを使用する。

【付記】骨量減少（骨減少）[low bone mass (osteopenia)]：骨密度が $-2.5SD$ より大きく $-1.0SD$ 未満の場合を骨量減少とする。

とともに、診断に際して用いる部位別・機種別にみた日本人男女におけるカットオフ値や、基準としての男女別・測定機種別の骨密度のYAM値・SD値などの詳細なデータが併せて記載されることを紹介した。

内科からみた診断基準改訂のポイント

今回の改訂は、診断基準が一般内科診療でもより広く活用されることを目的の一つとしている。杉本利嗣氏は内科の視点から、他の生活習慣病などの診断基準と比較して曖昧な点も少なくなかったこれまでの基準に、内科医から寄せられたさまざまな疑問や要望を紹介し、これらに添えてどのような改訂が行われたかを解説した。まず既存脆弱性骨折の部位によって骨折リスク因子としての重みが異なることから、新しい診断基準では骨折種の分類を明記した。さらに、脆弱性骨折の定義における“軽微な外力”や“骨折部位”が明確に示された。また、骨密度による診断は従来の「YAMの70%未満」からWHOの定義に合わせて「YAMの70%または $-2.5SD$ 以下」とされた。

さらに“骨量減少”は海外誌への論文投稿などに配慮して国際基準に合わせ「 $-2.5SD$ より大きく $-1.0SD$ 未満」と定義を変更し、骨粗鬆症の診断基準自体にはこれを含めないこととした。診療現場から多く要望が寄せられた「重症骨粗鬆症」や「骨折の危険性の高い骨粗鬆症」の定義については、現状では必ずしもエビデンスとコンセンサスが十分ではないことから明確な定義づけは避け、治療選択の際の参考となるように本文で国内外の知見を紹介するにとどめた。

杉本氏は、続発性骨粗鬆症の診断など今後課題を残してはいるものの、%とSD表示を併記することにより、国際的な整合性が図られた。また「骨粗鬆症の予防と治療ガイドライン2011年版」における薬物治療開始基準とも整合性が得られた改訂であるといえる、とまとめた。

骨密度測定をめぐって放射線科の視点から

診断基準の中心となる骨密度の測定に関して、改訂に際して浮き彫りになった問題点が曾根原喜氏から紹介された。基準としてのYAM値を

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-2.5SD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。曾根氏は，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

第 14 回日本骨粗鬆症学会シンポジウム REPORT

骨粗鬆症の予防と治療ガイドライン
2011 年版より引用改変

改訂版診断基準
による骨粗鬆症

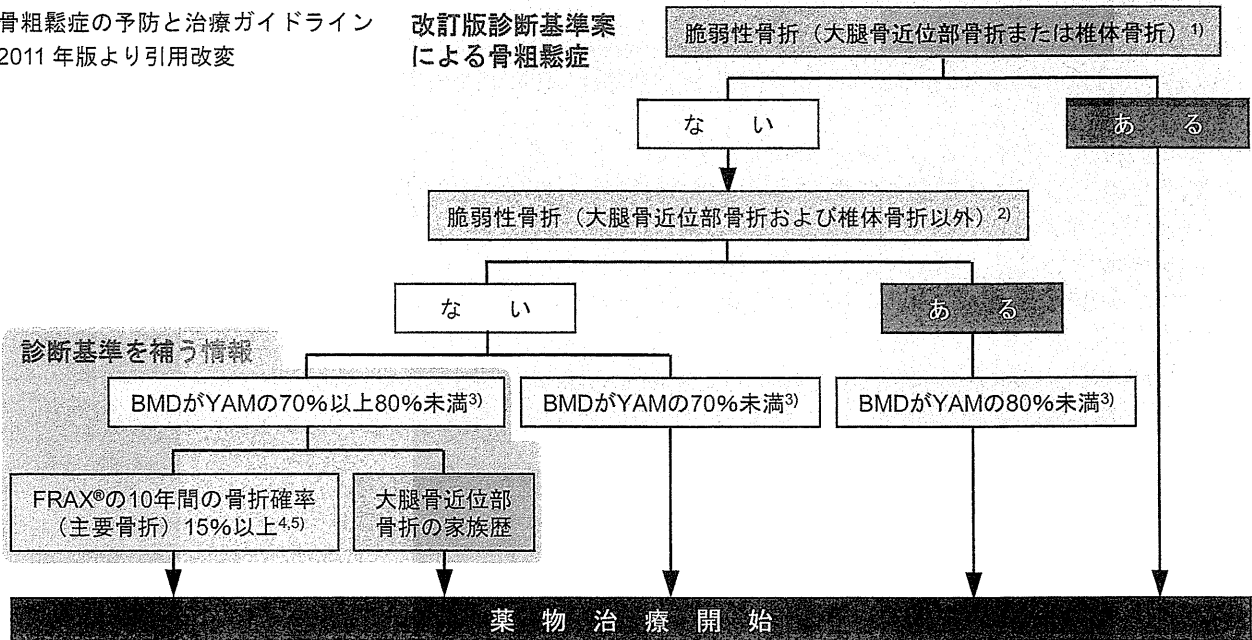


図 1 原発性骨粗鬆症の薬物治療開始基準と改訂版診断基準との関連性

- 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わないかとする意見も出たが、曾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。

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

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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 phosphatase (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.

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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 D₃ 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 ¹²⁵I 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 D₃ 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 D₃ 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 <i>n</i> =4,793	With vitamin D Deficiency <i>n</i> =3,443	Without vitamin D Deficiency <i>n</i> =1,350	<i>P</i> ^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 phosphatase, *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 <i>n</i> =4,793	DAS28 <2.6 <i>n</i> =1,817	DAS28 ≥2.6 <i>n</i> =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

^aEighteen 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 step-wise 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 D₃ dosage and vitamin D supplementation although alfalcidol 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.

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

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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

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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, EMBASE, 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.

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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 L₂₋₄ (a) and proximal femur (b). Data from Yoshimura [1] (Copyright © 2009 Springer Science + Business Media BV)

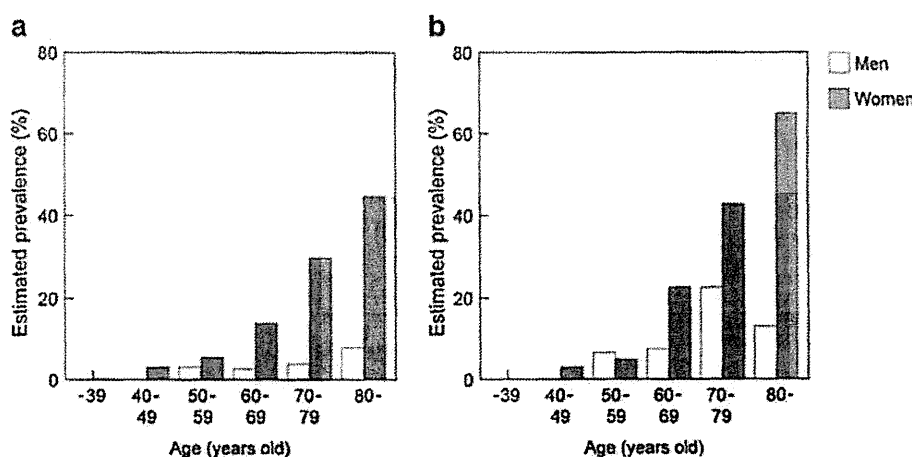
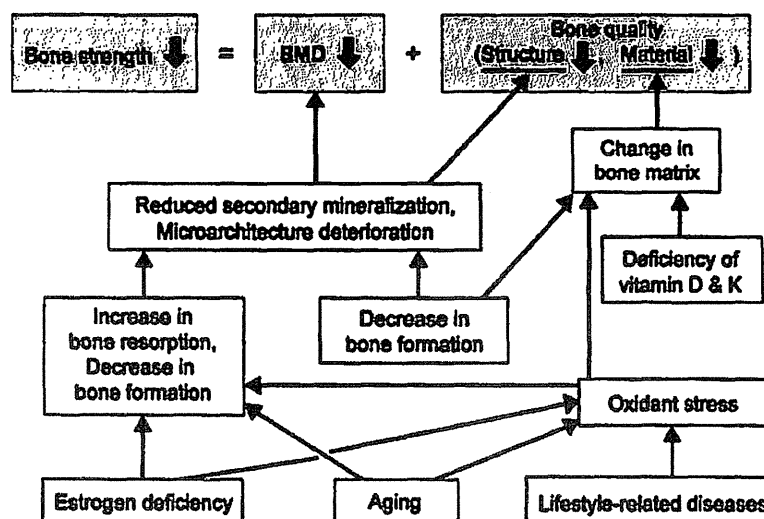


Fig. 2 Factors causing deterioration of bone strength



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

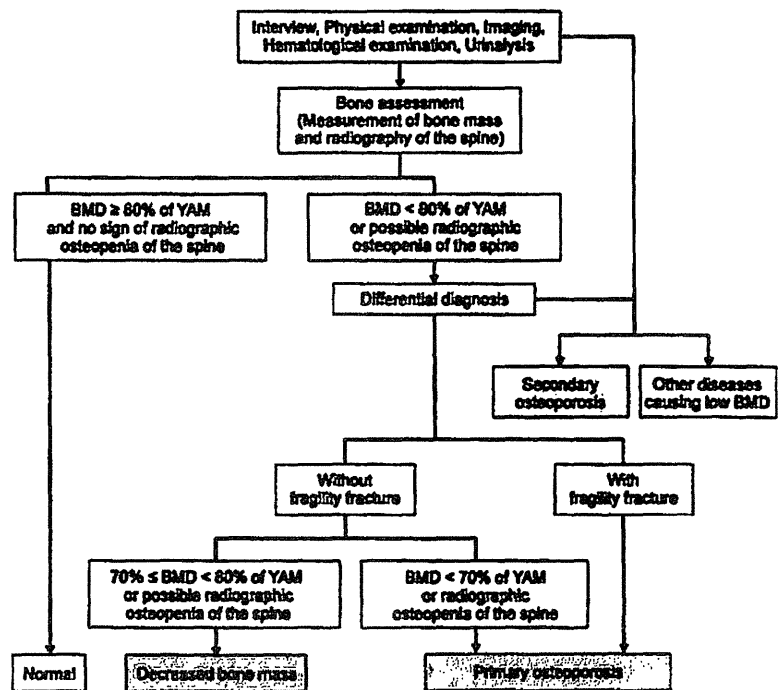
In the absence of a fracture, osteoporosis is nearly asymptomatic. However, patients with osteoporosis are predisposed to the development of fractures due to loss of bone strength, and the occurrence of fractures will severely impair their QOL (Fig. 4). Osteoporotic fracture is also called fragility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

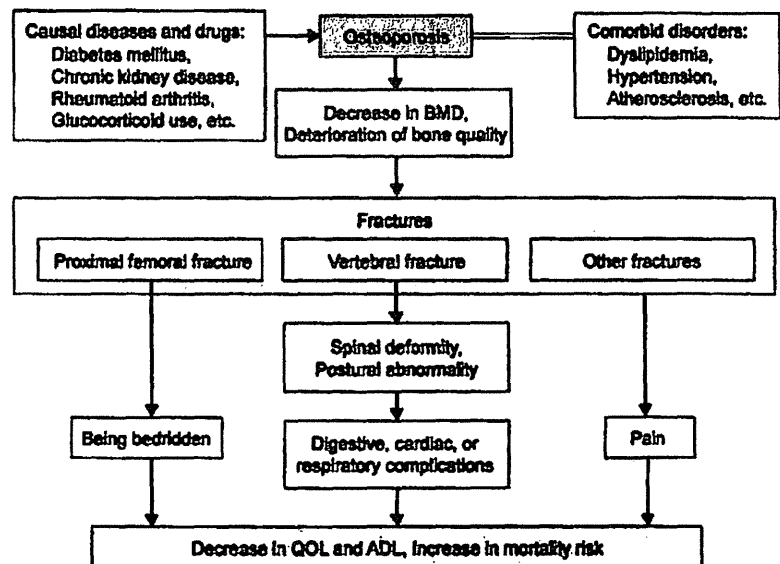
The objectives of the medical interview and physical examination are to assess the presence and symptoms of osteoporotic fractures, risk factors for osteoporosis and fractures, and to obtain information for the differential diagnosis.

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 semi-quantitative 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.