サルコペニア—筋研究の最前線—

村木 重之先生

は測れていないです．今筋量はインピーダンス法です．

斎藤　そうしますと握力とか下肢筋力は評価できるということですね．サルコペニアが起きて関節などの痛みが生じ，QOLが低下する．レントゲン上はOAの変化があっても痛みがない人はたくさんいらっしゃいます．また一方で，OA症例に運動療法を行うと臨床症状がよくなるという報告が散見されますが，ロードスタディからみても同じ方向性の結果がでているということですね．1998年に行われたDEXAをもとにしたサルコペニアの年代別罹患率に関しての報告をみてみますと，60歳代で20％前後ですが，80歳以降は50％に増えてくるとのことです．国立長寿医療研究センターのデータでは男性は年齢とともにサルコペニアの罹患率が増えてきますが，女性では，80代になってから増えてくるようです．男性のほうがサルコペニアになりやすいのでしょうか．男女差というのはいかがでしょうか．

原田　私どもの施設の周辺で住民票から無作為にとってきていただいた方では，それほど偏りがないと思いますが，おっしゃるように男女差は介護の状況とかバランスなどで，どの年代でも男女差があります．女性のほうが落ちている状況で低下していきますね．それは厳然した事実だと思います．ところがサルコペニアをDEXAで測ったデータで判定しますと，筋量で判定すると女性は最初から男性よりやや低いのですが，落ち方が緩やかであまり有意差がでない感じ．男性はトレンドがあって落ちる．男女の現れ方というのがずいぶん違う．そこに筋力とかパフォーマンスを合わせるとどうかわかりませんが．

斎藤　筋力自体も関連した動きですか．

原田　筋力はやはり落ちてきます．

斎藤　筋量と筋力のパフォーマンスに関しての傾向は男女とも同じと考えていいですか．

原田　筋量とパフォーマンスはあまり合わないのです．筋力とパフォーマンスは合いますが．筋量の示す意味は何だろうと考えさせられるところがありますね．

サルコペニア診断の現況と今後

斎藤　一般的にサルコペニアというと1998年に報告されたニューメキシコでの疫学データが用いられていますね．同研究では全身DEXAで測定した筋量のデータがよく用いられていますが，それを診断基準としていいかというのは今後の課題かもしれないですね．

原田　そうですね．ヨーロッパでの合意でも，アメリカでもスクリーニングのところで他の因子を入れてみますが，最終的な判定は筋量なのです．診断基準の最後にある確定診断に至るところでは筋量は必ず評価するので，そこと現実の結果が合わないのでそのまま進んでいいのだろうかと今思っているところです．

斎藤　確かにやせ細っていてもパワフルなお年寄りはいますね．そういう人たちは筋肉量が少ないからといって「あなたはサルコペニアです」といわれても「失礼な」と叱られるという感じでしょうね．

原田　そうです．先ほどのようなわれわれの近くの住民で24％ぐらいの受診者．男女両方とも25：25で変わっていないですね．

斎藤　全身DEXAからの筋肉量の評価と質的な評価，例えば簡便なインピーダンス法で評価することも重要と思います．また，握力測定も代用して，これらを総合評価してサルコペニアと診断するのが理想かもしれませんね．

原田　今はそのような流れは増えてきていますね．

斎藤　国内で診断といいますとどういうかたちでしていますか．

原田　日本ではそこはまだですね．

斎藤　国際的なコンセンサスはどうですか．

原田　ヨーロッパでは最初にパフォーマンスでスクリーニングして，それが落ちている人は筋量を測って診断する一方，あまり落ちていない人は握力など筋力を測って，カットオフ以下であれば筋量測定で診断するという仕組みです．最終的な判定は筋量というようになっています．

斎藤　筋力のパフォーマンスというのは具体的にどういったものですか．

原田　歩行速度などです．村木先生が詳しいと思います．

村木　ヨーロッパのコンセンサスでは歩行速度が0.8 m/秒以上か以下でまず入り口で分けて，それ以上だとその時点でサルコペニアではない．それ以下になるとまず握力を測って，握力が低い場合に次にさらに筋量を測って，筋量が低かったらサルコペニアと診断することになっています．

斎藤　ヨーロッパでこれだけしっかりしているということは，ヨーロッパではサルコペニアに関する研究が進んでいるということですか．

村木　進んでいるといっても本当に最近ですからね．ヨーロッパでもわれわれと同様に着目し始めたというところではないでしょうか．

斎藤　まさにこれからというところですね．今後具体的に健診レベルでサルコペニアをスクリーニングする．例えばパフォーマンス評価として歩行能力や握力，インピーダンス法を行い，骨密度測定で筋量を測るというようにシフトしていくといいですね．今後，サルコペニアもひとつの運動疾患として啓蒙していくべきだと思います．健診レベルでサルコペニアを拾い上げるにはどうしていったらいいと思われますか．

村木　健診レベルでは握力が簡便，かつ非常にいろいろなものにかかわっています．握力は全身筋力と相関が高いことも報告されていますので握力がスクリーニングとしてはいいと思います．握力というのも限界がありますので，そこからさらにスクリーニングで拾い上げたものを下肢筋力とか歩行速度，われわれは「片足立ち」や「椅子立ち上がり」などでみていますが，歩行速度が運動機能をみるうえではいろいろな意味で有効であるということがわかっています．将来の転倒しやすさなども歩行速度が非常に絡んできます．歩行速度をみて評価してくことが必要だろうと思います．

原田　私もそう思いますね．歩行速度は非常に重要な指標にもうすでになっていると思います．ヨーロッパも歩行速度でスクリーニングをしますし，アメリカでも歩行速度や歩行距離を取り上げていますね．私どもが今までそれを臨床でやれてこなかったのは10メートルの歩行速度です．助走とか入れると16メートル要るのです．そういうスペースを特別に設けるのは病院やクリニックでは大変です．そこに専従の人を置くというのも難しい．その点「開眼片足立ち」はスペース，人手的には容易にできますから，運動器機能判定で，片足立ちとTUG（Timed Up

& Go Test)が議論されたときには，歩行速度も重要な候補としてあがっていたようですが，やはり実用性の問題があって開眼片足立ちとTUGが残ったと聞いています．

斎藤　サルコペニアに関連するバイオマーカーの可能性というのはどうでしょう．

重本　今後，サルコペニアの指標に使えるバイオマーカーはおそらくいくつかでてくるだろうと期待しています．私たちもバイオマーカーの研究を進めています．臨床的に定義ができる3つのファクター，つまり筋力，筋量，パフォーマンス，これらの測定値を直接対象にしたバイオマーカーの探索はなかなか難しいと思います．研究サイドから考えると，筋組織の維持に関連した生物学的な可塑性の指標が有効なバイオマーカーになる可能性が高いでしょう．サルコペニアを含めて，エイジングは可塑性を失っていく過程であろうと私は捉えています．この可塑性を理解するには，神経筋シナプスがよい例です．マウスモデルを使い，ある一定の月齢まではシナプスの形態は保たれているのですが，エイジングに伴い形態が顕著に変化します．食事制限でエイジングによるシナプスの形態変化を予防できることや，また運動をさせればシナプスの形態が若い状態に戻るという報告があります．その分子メカニズムとして，シナプスを介して筋と運動神経の間で相互作用があることがわかってきています．もうひとつ私が注目していることは，筋肉の代謝調節機能です．今年，ハーバード大のSpiegelman教授のグループがアイリシンという新しいホルモンを報告しています．これは，筋肉から分泌され脂肪細胞に作用してエネルギー消費を誘導すると報告しています．私の知る限りではアイリシンというのは筋特異的に発現されますので，IL-6だとかTNF αというような非特異的な炎症性マーカーとは異なります．筋は運動機能だけでなく，環境変化に伴う代謝制御をしていますので，この点に着目したサルコペニアの指標も可能性があるのではないでしょうか．

斎藤　非常にprimitiveな質問で恐縮ですが，筋肉組織というのはニッチである基底膜も含めて新陳代謝が活発に行われているのでしょうか．

重本　筋線維単位でみれば比較的stableな状態にありますが，分子レベル，蛋白とかというレベルでは非常にactiveに代謝しています．

斎藤　骨などでは海綿骨では年間40％は新陳代謝により入れ替わりますが，マクロな視点からみた筋肉の新陳代謝というのはどうでしょう．

重本　それはもちろん，サテライト細胞が筋線維に分化して補充をしているということが起きていると思います．しかし，疾患のない正常な筋組織で，サテライト細胞が筋に分化する過程をリアルタイムイメージングで直接みたという報告を私はまだみたことがありません．興味あるポイントです．

斎藤　新陳代謝が止まった組織というのは薬剤で介入してもなかなか若い頃の状態に戻すチャンスは少ないわけですが，筋肉では新陳代謝が旺盛に行われているのであれば，どの時点から治療介入をしても改善し得ると考えてよろしいですか．

重本　筋肉は，筋だけでなく由来の異なるさまざまな細胞が非常に複雑な相互作用を行うことで維持されています．サルコペニアの初期の段階ではそれぞれの変化は大きくないかもしれませんが，筋萎縮に進むと修復するのは非常に難しい臓器であると思います．

サルコペニア治療の現況と今後

斎藤　サルコペニアになる方をなるべく早くみつけて，将来のリスクを評価するバイオマー

重本 和宏先生

カーや非侵襲的な検査方法を確立して，早期介入することが大事ということになりますね．治療という面では研究はどこまで進んでいるのでしょうか．

重本　臨床の先生が運動と栄養に着目して予防や治療に関する研究を実際に精力的に進めておられると思いますが，私も同じ考えです．ただし，運動のプロトコールについて，いろいろな考え方があるようです．栄養については，ロイシンやバリンなどの分枝アミノ酸による筋の代謝制御の機構がわかってきており，その成果に基づく予防法の開発が行われています．例えば，分枝アミノ酸の投与方法については，シグナル伝達の解析からパルス投与がよいといっておられる研究者もおられます．運動，栄養による新しい予防の開発の可能性は十分残されていると思います．しかし，先ほど申しましたように可塑性をいったん失ってしまった場合には何をいくらやっても難しいと思います．

斎藤　できるだけ早く介入しなくてはいけないということですね．男性例に対してはアンドロゲン投与により筋力は変わらないが筋量が増えたとする報告があります．また，ミオスタチン（アンドロゲン受容体モジュレーター）を使うと筋量が増えるといったようなデータもあるようですが，これらの薬剤介入は可塑性が失われてからでも効果は期待できるのでしょうか．

重本　これはいってみれば“鶏が先か卵が先か”という話ですが，私たちは可塑性に関する生物学的なメカニズムをもっと知らなくてはなりません．老化マウスを観察すると，ある月齢から筋肉や運動神経細胞の顕著な病理学的変化が起きます．臨床の先生たちとお話をしてもお年寄りの方も急激にパフォーマンスが落ちてくるということをおっしゃっています．何か可塑性を失ってしまう臨界点のようなものがあるのではないかと考えています．

斎藤　村木先生にお伺いしたいのですが，多くの患者さんを診ておられて運動習慣のある人といいましょうか，日常生活を活発にしていてもサルコペニアにはなってしまうのでしょうか．

村木　それは防ぎ得ると思います．患者さんに運動習慣を聞いていますが，普段から運動習慣のある人は明らかに筋力があるし，元気だから運動しているということもあると思います．防ぎ得るし，運動と栄養で防ぐしかないと思いますので，しっかり運動するということが予防につながる唯一の方法ではないかと思います．

斎藤　原田先生は整形外科医の立場から運動や栄養以外に薬剤なども視野にあると思います．先生の率直なお考えは運動，栄養を早めに介入することがベストというお考えでしょうか．

原田　運動，栄養で予防できればそれが一番いいと思います．しかし，積極的で治療介入となってくると，薬剤の候補がでてきつつあるようですから，そういう面では今後はかなり発展してくるのではないでしょうか．それと，転倒をひとつのイベントとしてサルコペニアの評価としている場合もかなりあります．それをみますと高齢者の方でも，一定の筋力バランス運動をした場合に転倒をアウトカムにおいて解析すると，運動療法は高いレベルで有効性があると

思います．薬剤になると難しいところがあります．筋力に対してビタミンDを投与するようなRCT（無作為化比較試験）もたくさんあります．それは上肢の筋力も下肢の筋力にも全体的にはあまり有効でなかったという結果だったと思います．

斎藤　論文などによるとビタミンDの貯蔵状態を反映する25ビタミンDの数値が20を切っていると将来の筋力減少のリスクが高いといった報告もあります．ロードスタディでは，ビタミンDを含めた栄養指標やバイオマーカーがサルコペニアの評価，また予測に役立ちそうだという結果は得ていますでしょうか．

村木　今のところ筋量とマーカーについてはいろいろやっていますが，積極的なデータはでていないのが現状です．今後さらに追っていくことでまた新たなことがいえるかもしれませんが，現状では残念ながらないですね．

斎藤　栄養摂取の問題も重要に思いますが，特にビタミンDと転倒リスク，筋力の問題は注目すべきと思いますが，何かその点で原田先生，データはございますでしょうか．

原田　その点に対するひとつのヒントになるかどうかわかりませんが，私どものところでは全身骨で骨量測定を続けていまして，骨粗鬆症を患者の筋量の経年的データがあります．それをレトロスペクティブに解析すると，活性型ビタミンDの投与が1年間で筋量が上昇する群がありました．筋力は測定できていません．サルコペニアの範疇に入るような患者がそのような増加を示しました．ビタミンD不足が背景としてあるのかもしれません．

斎藤　ビタミンD（25OH D）の測定は保険適応の一歩手前まできているようですね．骨の評価だけではなく，サルコペニアを評価するうえで広い意味でのサロゲートマーカーとして使える可能性があるということですね．

原田　評価できるようになるといいと思います．いままでの患者さんもD不足かどうか判定できていないですね．

まとめ

斎藤　今後の予防や治療法の確立という観点でお考えがありましたらお願いします．

重本　基礎研究の立場から，筋萎縮の原因疾患によって筋線維タイプの変化が異なる点に興味があります．サルコペニアでは遅筋が増えるということがわかっています．画像診断で筋量だけでなく筋肉の質的な変化を定量するなんらかの方法があれば，診断や予防に役立つのではないかと考えています．

斎藤　そうですね．量の変化と質の変化をMRIやエコーで評価できるとよいですね．同時にバイオマーカー，これらが揃うといいのではないかと思います．

原田　歩行速度は非常に重要ですが，臨床に取り入れる際に難点があります．そのような運動機能を測定しやすい診療環境を整えることが今後重要と考えます．ちょうど明日からですが，ロコモ外来という名称の外来整備をして，その一角に運動機能検査室を作りました．筋力，歩行速度などを測定する予定です．

斎藤　村木先生はいかがでしょうか．

村木　運動の評価として，歩行速度，片足立ちも40～50歳代の若い人だとほとんど60秒台ですね．早期に見極める早期診断が大事ということで，片足立ち以外に何かとわれわれが考えているのは「立ち上がり」です．椅子から立ち上がるというのは以前から評価しています．例えば40 cmぐらいから両足で立ち上がれるか．片足で立ち上がれるか．40 cmで大丈夫なら30 cm，20 cmという具合に．これからやっていく話で

左より，斎藤充先生，村木重之先生，原田敦先生，重本和宏先生

すが若年者でも良い人と悪い人がでてくるのではないか．そういうところで見極めて早期の評価ができるのではないかと思って今後考えています．

斎藤　今後サルコペニアという疾患概念を全国的に普及しなくてはと思いました．将来的にはガイドラインといったものをつくらなければいけないかと思います．サルコペニアの診断基準が海外には存在するということは以外と知られていません．私も勉強不足で知りませんでした．しかし全身DEXAで評価できるというのであれば，過去のデータにさかのぼり研究してくださる先生方も増えるように思います．

原田　ロコモの有用性は認識され始めていますが，筋肉の機能低下がどんなロコモに結びつくのかなど，筋肉については整形外科医の認知は低いと思います．そこにサルコペニアが潜んでいるという見方がもう少し広がれば，筋量測定はDXAやバイオインピーダンス法で可能なので，興味を持って取り組んでくださる先生方もこれから増えるのではと期待しています．その際に，骨粗鬆症と同じく，多くの診療などの学際的な取り込みになると思います．

斎藤　今日は先生方からさまざまなご意見をいただいて大変勉強になりました．サルコペニアの概念を知っていただき，老人性虚弱の撲滅を目指したいと思う整形外科医が増えてくれることを祈ってやみません．今回はゲストエディターとして原田先生をお招きし，この分野でトップランナーの先生方にお話いただきました．今日はありがとうございました．

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BRIEF REPORT

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 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

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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 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.

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References

1. Baker JF, Baker DG, Toedter G, Shults J, Von Feldt JM, Leonard MB (2012) Associations between vitamin D, disease activity, and clinical response to therapy in rheumatoid arthritis. Clin Exp Rheumatol 30:658–664
2. Braun-Moscovici Y, Toledano K, Markovits D, Rozin A, Nahir AM, Balbir-Gurman A (2011) Vitamin D level: is it related to disease activity in inflammatory joint disease? Rheumatol Int 31:493–499
3. Craig SM, Yu F, Curtis JR, Alarcon GS, Conn DL, Jonas B, Callahan LF, Smith EA, Moreland LW, Bridges SL Jr, Mikuls TR (2010) Vitamin D status and its associations with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. J Rheumatol 37:275–281
4. Haque UJ, Bartlett SJ (2010) Relationships among vitamin D, disease activity, pain and disability in rheumatoid arthritis. Clin Exp Rheumatol 28:745–747
5. Kerr GS, Sabahi I, Richards JS, Caplan L, Cannon GW, Reimold A, Thiele GM, Johnson D, Mikuls TR (2011) Prevalence of vitamin D insufficiency/deficiency in rheumatoid arthritis and associations with disease severity and activity. J Rheumatol 38:53–59
6. Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D (2007) Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum 56:2143–2149
7. Rossini M, Maddali Bongi S, La Montagna G, Minisola G, Malavolta N, Bernini L, Cacace E, Sinigaglia L, Di Munno O, Adami S (2010) Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. Arthritis Res Ther 12:R216
8. Varenna M, Manara M, Cantatore FP, Del Puente A, Di Munno O, Malavolta N, Minisola G, Adami S, Sinigaglia L, Rossini M (2012) Determinants and effects of vitamin D supplementation on serum 25-Hydroxy-vitamin D levels in patients with rheumatoid arthritis. Clin Exp Rheumatol 30:714–719
9. Welsh P, Peters MJ, McInnes IB, Lems WF, Lips PT, McKellar G, Knox S, Michael Wallace A, Dijkmans BA, Nurmohamed MT, Sattar N (2011) Vitamin D deficiency is common in patients with RA and linked to disease activity, but circulating levels are unaffected by TNFalpha blockade: results from a prospective cohort study. Ann Rheum Dis 70:1165–1167
10. Turhanoglu AD, Guler H, Yonden Z, Aslan F, Mansuroglu A, Ozer C (2011) The relationship between vitamin D and disease activity and functional health status in rheumatoid arthritis. Rheumatol Int 31:911–914
11. Haque UJ, Bathon JM, Giles JT (2012) Association of vitamin D with cardiometabolic risk factors in rheumatoid arthritis. Arthritis Care Res (Hoboken) 64:1497–1504
12. Song GG, Bae SC, Lee YH (2012) Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. Clin Rheumatol 31:1733–1739
13. Hayashibara M, Hagino H, Katagiri H, Okano T, Okada J, Teshima R (2010) Incidence and risk factors of falling in ambulatory patients with rheumatoid arthritis: a prospective 1-year study. Osteoporos Int 21:1825–1833
14. Furuya T, Hosoi T, Saito S, Inoue E, Taniguchi A, Momohara S, Yamanaka H (2011) Fracture risk assessment and osteoporosis treatment disparities in 3,970 Japanese patients with rheumatoid arthritis. Clin Rheumatol 30:1105–1111
15. Furuya T, Inoue E, Hosoi T, Taniguchi A, Momohara S, Yamanaka H (2012) Risk factors associated with the occurrence of hip fracture in Japanese patients with rheumatoid arthritis: a prospective observational cohort study. Osteoporos Int, in press
16. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Kobashigawa T, Ichikawa N, Tanaka E, Momohara S, Nakajima A, Hara M, Tomatsu T, Yamanaka H, Kamatani N (2007) Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: a prospective 54-month observational study. J Rheumatol 34:303–310
17. Furuya T, Yamagiwa K, Ikai T, Inoue E, Taniguchi A, Momohara S, Yamanaka H (2009) Associated factors for falls and fear of falling in Japanese patients with rheumatoid arthritis. Clin Rheumatol 28:1325–1330
18. Matsuda Y, Singh G, Yamanaka H, Tanaka E, Urano W, Taniguchi A, Saito T, Hara M, Tomatsu T, Kamatani N (2003) Validation of a

Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. Arthritis Rheum 49:784–788
19. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
20. Ohta H, Kuroda T, Onoe Y, Orito S, Ohara M, Kume M, Harada A, Tsugawa N, Okano T, Sasaki S (2009) The impact of lifestyle factors on serum 25-hydroxyvitamin D levels: a cross-sectional study in Japanese women aged 19–25 years. J Bone Miner Metab 27:682–688
21. Nakamura K (2006) Vitamin D insufficiency in Japanese populations: from the viewpoint of the prevention of osteoporosis. J Bone Miner Metab 24:1–6
22. Bogh MK, Schmedes AV, Philipsen PA, Thieden E, Wulf HC (2010) Vitamin D production after UVB exposure depends on baseline vitamin D and total cholesterol but not on skin pigmentation. J Invest Dermatol 130:546–553
23. Perez-Castrillon JL, Vega G, Abad L, Sanz A, Chaves J, Hernandez G, Duenas A (2007) Effects of Atorvastatin on vitamin D levels in patients with acute ischemic heart disease. Am J Cardiol 99:903–905
24. Jesudason D, Need AG, Horowitz M, O'Loughlin PD, Morris HA, Nordin BE (2002) Relationship between serum 25-hydroxyvitamin D and bone resorption markers in vitamin D insufficiency. Bone 31:626–630
25. Adami S, Bertoldo F, Braga V, Fracassi E, Gatti D, Gandolini G, Minisola S, Battista Rini G (2009) 25-hydroxy vitamin D levels in healthy premenopausal women: association with bone turnover markers and bone mineral density. Bone 45:423–426

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POSITION PAPER

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, 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.

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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-

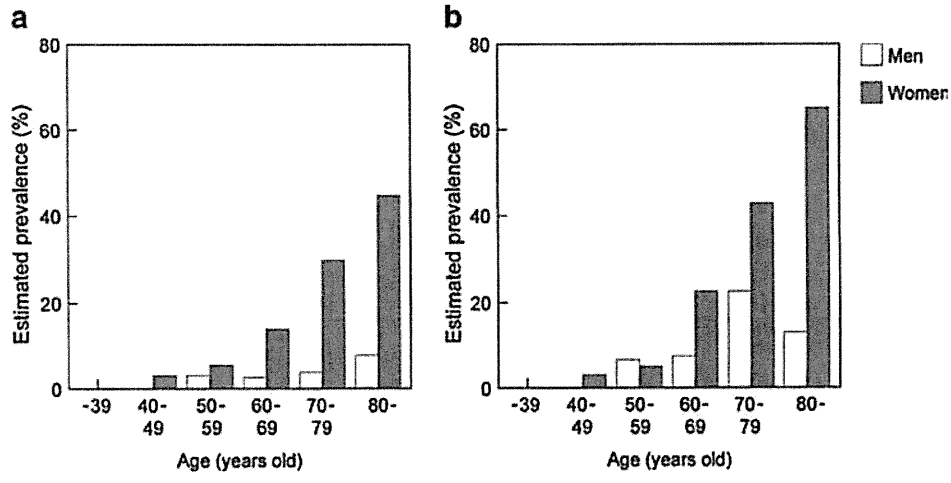

Fig. 1 Estimated prevalence of osteoporosis in Japan. Osteoporosis was diagnosed from BMD at vertebrae L_{2-4} (a) and proximal femur (b). Data from Yoshimura [1] (Copyright© 2009 Springer Science + Business Media BV)

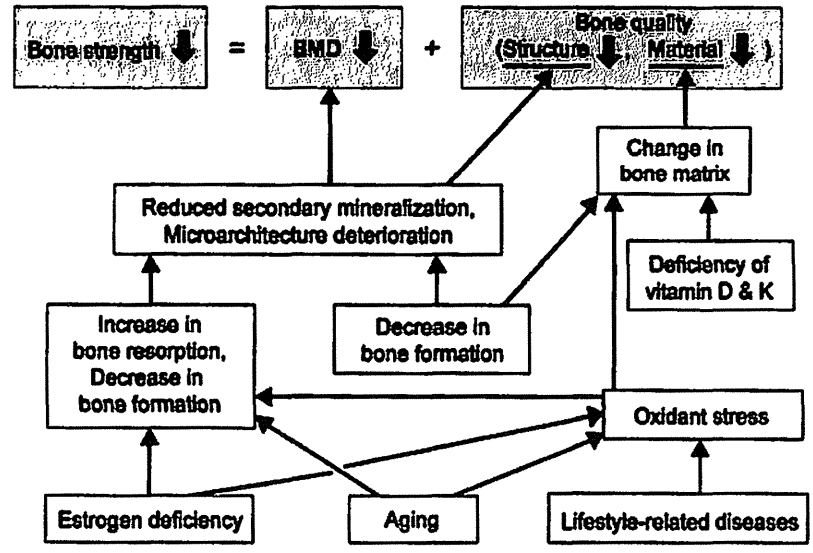

Fig. 2 Factors causing deterioration of bone strength

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.

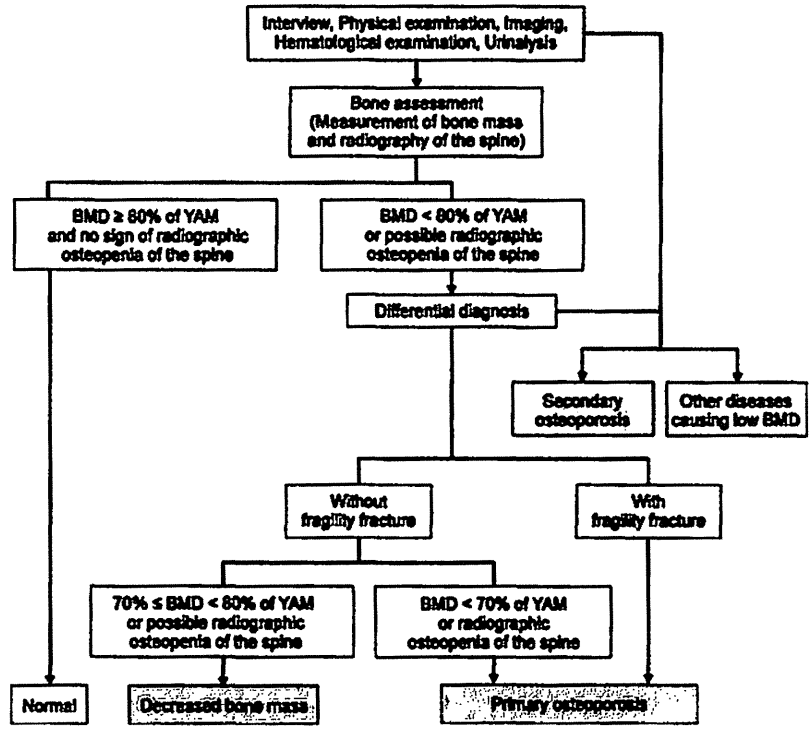

Fig. 3 Procedure for the diagnosis of osteoporosis. *YAM* young adult mean (20 to 44 years of age). Adapted from Orimo [4] (Copyright© 2001 Springer Science + Business Media BV)

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.

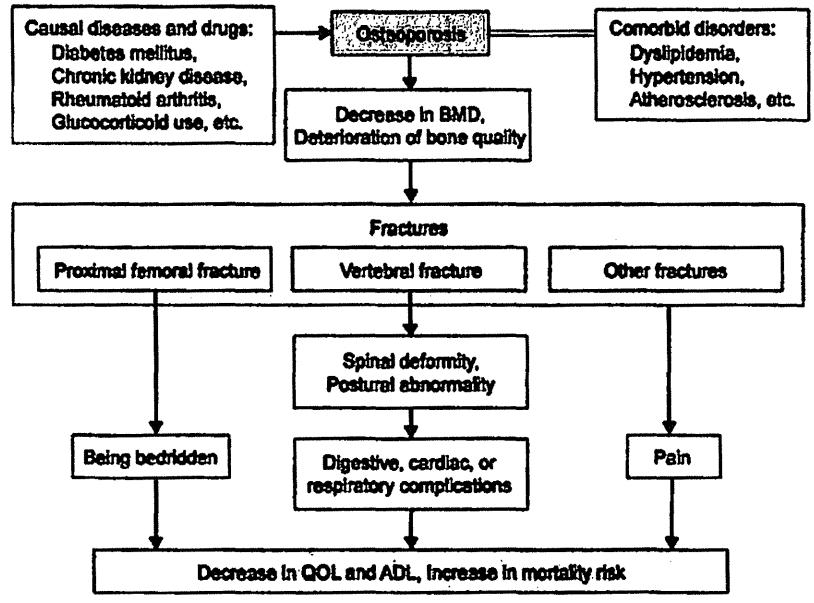

Fig. 4 Clinical presentation and prognosis of osteoporosis

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.

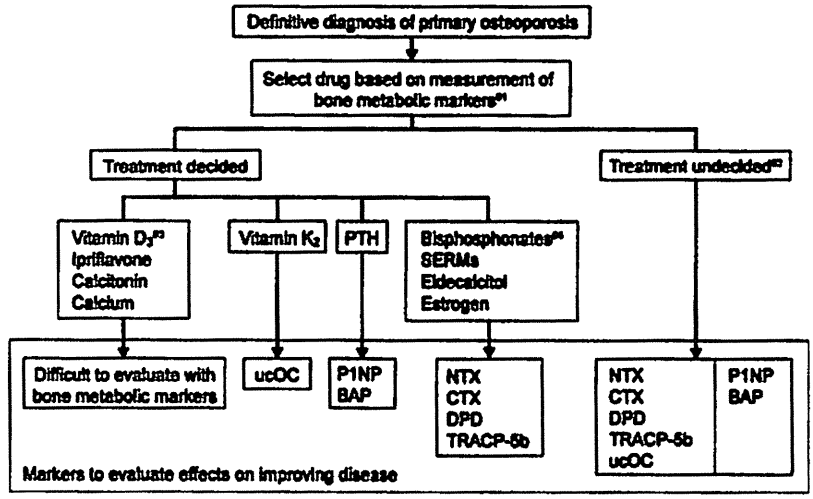

Fig. 5 Measurement of bone metabolic markers in drug treatment of osteoporosis. #1: in patients taking bisphosphonates, measure after stopping drug for at least 6 months, and in patients taking other osteoporosis drugs, measure after stopping drug for at least 1 month. #2: measure one type each of a 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].

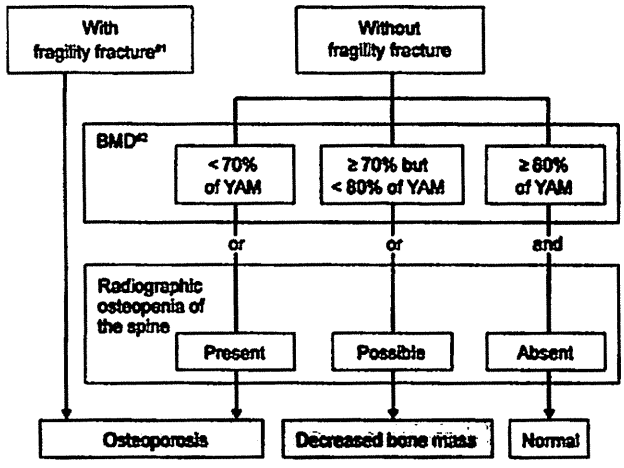

Fig. 6 Diagnostic criteria for primary osteoporosis (updated in 2000). Primary osteoporosis is diagnosed according to these criteria in the absence of diseases causing low bone mass or secondary osteoporosis. #1: fragility fracture is a nontraumatic bone fracture that is caused by slight external force 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.