表3　低骨量および骨粗鬆症に伴う骨折の危険因子

低骨量の危険因子
高年齢，女性，痩せ，家族歴，運動不足，喫煙，過度のアルコール摂取，女性ホルモン不足状態（遅い初経，無月経，早い閉経），カルシウム不足，ビタミンD・K不足，胃切除，副腎皮質ステロイドの服用，甲状腺機能亢進症，副甲状腺機能亢進症，糖尿病，肝，腎不全
骨粗鬆症に伴う骨折の危険因子
低骨量，過去の骨折歴，高年齢，やせ，認知症，運動機能障害，視力障害の合併，睡眠薬，血圧降下薬

（文献1）より引用）

まとめ

骨粗鬆症では骨代謝学会骨粗鬆症診断基準を念頭において，骨折リスクとリスク病態に関する内容を聴取し，総合的，包括的な診断と治療をすすめることが重要である．

文 献　1）日本骨代謝学会 骨粗鬆症診断基準検討委員会：原発性骨粗鬆症の診断基準（2000年度改訂版）．日骨代謝会誌 18:76-82，2001
2）骨粗鬆症の予防と治療のガイドライン作成委員会：骨粗鬆症の予防と治療のガイドライン，2006年版．ライフ・サイエンス社，2006
3）高橋栄明，他：骨粗鬆症患者QOL評価質問表．日骨代謝会誌 18:83-101，2001
4）岩谷　力，他：OPACによる骨粗鬆症患者のQOL評価．日骨代謝会誌 17:136-140，2000
5）徳永邦彦，他：円背が骨粗鬆症患者のQuality of Lifeに及ぼす影響．Osteoporosis Japan 9:480-484，2001
6）Nawata H, et al.:Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research. J Bone Miner Metab 23:105-109, 2005
7）日本骨粗鬆症学会 生活習慣病における骨折リスク評価委員会：生活習慣病における骨折リスクに関する診療ガイド．ライフ・サイエンス社．2011
8）中村耕三，他：整形外科臨床パサージュ4　骨粗鬆症のトータルマネージメント．中山書店，2010
9）遠藤直人：骨粗鬆症のすべて．南江堂，2007
10）日本整形外科学会：ロコモティブシンドローム診療ガイド．文光堂，2010

著者連絡先　（〒951-8510）新潟県新潟市中央区旭町通1番町757
新潟大学大学院医歯学総合研究科機能再建医学講座整形外科学分野　遠藤直人

Geriat. Med. 49(9)：1017～1021, 2011

Seminar

2．骨粗鬆症の新しい治療法
4）新しい活性型ビタミンD製剤の意義と使い方

遠藤 直人

KEY WORD

- 25(OH)D
- 骨折危険因子
- エルデカルシトール
- 脊椎骨折
- 大腿骨頸部/転子部骨折

SUMMARY

血清25(H)Dはビタミンの充足度を示す指標である．ビタミンD不足は骨粗鬆症，骨折の危険因子であり，骨折発生率が高い高齢者では，ビタミンDの充足あるいは不足かについての評価とそれに基づく対策が必要である．

新しいビタミンD製剤：エルデカルシトール：2β-(3-hydroxypropoxy)-calcitriolは，カルシウム代謝のみならず骨代謝異常を改善する点で新規性が高い薬剤であり，1,25(OH)$_2$Dに比して，骨密度への増加効果は大きく，新規脊椎椎体骨折の発生頻度に対する効果は相対リスクを26%低減させるものであった．また非椎体骨折，なかでも前腕骨骨折の有意な抑制を示している．

はじめに

骨粗鬆症は「骨折リスクを増すような骨強度上の問題を既にもっている人に起こる骨格の疾患」(2000年のNIHコンセンサス会議)で，骨の脆弱化により骨折を来す．『骨粗鬆症の予防と治療のガイドライン2006年版』では，骨粗鬆症の予防と治療の目標は「骨格の健康を保ち，身体の健全な形態と運動性を維持し，骨折を予防すること」である[1-3]．ここでは骨折危険因子としてのビタミンD不足に注目し，さらに骨折予防効果の大きい新しいビタミンD製剤の意義，使い方に焦点を当てる．

ビタミンD不足と骨粗鬆症

ビタミンDは食物からの摂取と皮膚での合成を経て，肝臓にて25(OH)Dに変換される．その後，腎臓で水酸化され，1,25(OH)$_2$D(活性型ビタミンD)に変換される．ビタミンDは小腸におけるカルシウム，リンの吸収を促進し，副甲状腺(上皮小体)に作用してホルモン(PTH)の合成・分泌を抑制し，さらに尿細管におけるカルシウム再吸収を促進する．したがって骨粗鬆症における骨代謝，病態把握においてビタミンDが充足しているか，否かは重要な情報である[3,4]．

えんどう なおと(新潟大学大学院医歯学総合研究科機能再建医学講座整形外科学分野(医学部整形外科学教室)

血液中25(OH)Dレベルの評価の意義

血清25(H)Dはビタミンの充足度を示す指標である．30 ng/mLよりも低値になるに伴い，PTH値が上昇することおよび骨組織所見から，30 ng/mLを充足・不足の閾値としている．一方，20 ng/mLを閾値としている報告もある[5-7]．

Pfeiferらは閉経後女性237名において，血液中25(OH)レベルと体幹動揺性が負に相関すること[8]，Steinらは，転倒経験のある方は転倒経験のない方に比して血液中25(OH)レベルが低値であること[9]，Nuttiらは，大腿骨頸部骨折患者は血液中25(OH)Dが低値である[10]ことを報告した．またSakumaらは，新潟県佐渡市(総人口70,011名，高齢化率34%，2004年)で調査し，大腿骨頸部/転子部骨折症例の血液中25(OH)Dは対照(骨折のない方)に比して低値であることを報告した[6,11,12]．さらに佐渡市，愛知県，鳥取県，熊本県において同時調査を行い，大腿骨頸部/転子部骨折例とともに脊椎骨折例においても同様に低値であることを示した[13]．さらに，橈骨遠位端骨折がビタミンD不足と関連しているとの報告もある[14]．骨粗鬆症関連骨折である大腿骨頸部/転子部骨折，脊椎骨折，橈骨遠位端骨折でビタミンD不足と関連していることは，ビタミンD不足が骨粗鬆症性脆弱骨折，骨脆弱性の危険因子であることを示している[6,13,14]．さらにSuzukiらは活動性[15]，Kurodaらは生命予後[16]と関連することを報告した．ビタミンDの筋肉への影響と合わせて考えると，ビタミンD不足⇒筋力低下，活動性低下⇒転倒⇒骨折へと，間接的にも骨折に関係していることが推察される．さらに認知機能障害・改善との関連が近年，示唆されていることから，ビタミンDの多様な作用および加齢との密接な関連がうかがわれる[17-22]．

岡野らの報告では日本人ではビタミンDが多くの国民で不足しており，特に80歳以上では70%の方が不足と報告している[4,5]．

以上より，ビタミンD不足は骨粗鬆症，骨折の危険因子であり，骨折発生率が高い高齢者では，ビタミンDの充足あるいは不足かについての評価と，それに基づく対策が必要であると考えられる[5,6,12,14]．しかし，現時点では血液中25(OH)D測定は骨粗鬆症としての保険適応はないため，診療現場での測定には限界がある．

ビタミンDの臨床

日本では天然型ビタミンDは医薬品として処方されていない．活性型ビタミンDである1α(OH)D_3と1α25(OH)$_2D_3$が骨粗鬆症の薬剤として，またビタミンD補充としても処方されている現状である．

ビタミンDは「特にカルシウム不足が主体になっている症例や，転倒頻度が高く，骨折を起こしやすい高齢者への使用」が推奨されている(骨粗鬆症の予防と治療ガイドライン，2006年版)[3]．日本人ではカルシム摂取が少なく，高齢者では腸管からのカルシウム吸収能の低下，腎におけるビタミンD活性化能の減弱，二次的にPTH分泌亢進があることから，ビタミンDが期待される[3]．

骨密度，骨折予防効果について

臨床的にはビタミンDの骨密度増強効果は弱い．骨折予防効果については，ビタミンDの脊椎椎体骨折防止効果が報告されている．8試験(1,130患者総数，Pooled estimate)をメタ解析した結果，相対骨折リスクが0.63(0.45～0.88，$p<0.01$)であった[23-25]．Tilyardらの報告では既存の椎体骨折患者，全例女性392名を対象に3年間ビタミンDを投与した結果，非投与群に比して椎体骨折が低減した[26]．非椎体骨折については，6試験併合(6,187患者総数，Pooled estimate)では相対骨折リスク0.77(0.57～1.04，$p=0.09$)であり，抑制傾向のみで有意とまではいえない[5-8]．一方，Tanizawaらは新潟県佐渡島の住民11,377名を対象に調査し，ビタミンD服用者は大腿骨頸部/転子部骨折発生が非服用者に比して低いこと，ビタミンD服用中止に

より，骨折発生率は非服用者と同等レベルにまで高まることを報告した[27]．

これらの結果からビタミンDは，脊椎骨折，大腿骨頸部/転子部骨折を予防する効果があるといえよう[28-31]．

エルデカルシトール

骨密度増加については，わずかな増加効果がある新しいビタミンD製剤：エルデカルシトール：2 β-(3-hydroxypropoxy)-calcitriol はカルシウム代謝のみならず骨代謝異常を改善する点に新規性のある薬剤であり，1,25(OH)$_2$D に比して，ビタミンD結合タンパクへの結合能は高く，一方ビタミンD受容体への親和性は弱く，PTH 分泌抑制作用も弱い．

骨密度への増加効果は大きく，3年間で腰椎，大腿骨近位部での変化率はそれぞれ 3.3%，2.7%と有意に高いものであり，また新規脊椎椎体骨折の発生頻度に対する効果は相対リスクを26%低減させるものであった．さらに非椎体骨折，なかでも前腕骨骨折の有意な抑制を示した．その相対リスク 71%減少を示した．この試験における対照はアルファカルシドール服薬群であり，アルファカルシドールそのものは現在，ビタミン製剤として広く使われており，骨密度増加効果は大きくないものの，骨折予防効果があることは臨床の場でも実感しているところである．したがって上記の両者の比較試験結果は，エルデカルシトールがアルファカルシドールを上回る骨折予防効果を有していることを示すものである．さらにこの効果は 25(OH)D の値にかかわらず，ほぼ同等の効果を示した．

エルデカルシトールは骨代謝マーカーである尿中 NTX 値を下げ，骨形成マーカー値を抑制する結果を示した．副作用として，尿中カルシウム増加や血液中カルシウム上昇などが報告されている．またラット骨折モデルの骨折治癒過程に対する影響を検討した結果では，形状，骨折治癒に影響を示さなかったと報告されている[32]．

エルデカルシトールの使い方：適応と注意点

1）現在，活性型ビタミンD製剤を使われている方：現在の活性型ビタミンD(アルファカルシドール)以上の骨折抑制効果を有していることから，現在の活性型ビタミンD治療の適応者にはエルデカルシトールの適応がある．むしろ切り替えることも考えられる．

2）骨吸収亢進状態：骨吸収抑制作用があり，実際吸収マーカー値を下げることが明らかになっていることから適応と考えられよう．その際，吸収亢進状態，程度，要因を考え，強力な骨吸収抑制作用をもつビスホスホネートとの使い分けを考慮する．

今後の課題

・A-top 研究でビタミンDとビスホスホネートとの併用が報告されているエルデカルシトールについてもビスホスホネートと同様な併用効果が期待されるが，現時点で臨床例が明らかでなく，報告されることを待ちたい．

・いつの時点で使用開始するかについても検討を要しよう．脊椎骨折は大腿骨頸部/転子部骨折のリスクである．初発の脊椎骨折を予防することは，その後の骨折の連鎖を予防することにもつながる．骨粗鬆症の方をスクリーニングし骨折リスクを評価し，積極的に骨折予防することが必要であり，その対策としてビタミンDは有用な1つの方法であろう．

まとめ

ビタミンD不足への対応は重要である．新規ビタミンは骨折予防効果が高く，期待される．

文　献

1）遠藤直人：骨粗鬆症における骨折の特徴と治療・予防．Osteoporosis Japan　15：74-75，2007.

2）Morita Y et al：The incidence of cervical and trochanteric fractures of the proximal femur

in 1999 in Niigata Prefecture, Japan. J Bone Miner Metab **20**：311-318, 2002.
3) 骨粗鬆症の予防と治療ガイドライン作成委員会(代表　折茂　肇)：骨粗鬆症の予防と治療ガイドライン2006年版，ライフサイエンス出版，東京，2006.
4) ビタミンDの食事摂取基準　日本人の食事摂取基準(概要).
http://www.mhlw.go.jp/houdou/2004/11/h1122-2c.html
5) 岡野登志夫ほか：高齢者を中心とした日本人女性のビタミンD栄養状態と骨代謝関連指標について．Osteoporosis Japan **12**：77-79, 2004.
6) Sakuma M et al：Vitamin D and intact PTH status in patients with hip fracture. Osteoporos Int **17**：1608-1614, 2006.
7) Piemel M et al：Bone mineralization defects and vitamin D deficiency：histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydoxyvitamin D in 675 patients. J Bone Miner Res **25**：305-312, 2010.
8) Pfeifer M et al：Vitamin D status, trunk muscle strength, body sway, falls, and fracture among 237 postmenopausal women with osteoporosis. Exp Clin Endocrnol Diabetes **109**：87-92, 2001.
9) Stein M et al：Falls relate to vitamin D and parathyroid hormone in an Australian nursing home and hostel. J Amer Geriatr Soc **47**：1195-1201, 1999.
10) Nutti R et al：Vitamin D status and bone turnover in women with acute hip fracture. Clin Orthop **422**：208-213, 2004.
11) Sakuma M et al：Changes in Serum 25-hydroxycholecalciferol and Intact Parathyroid Hormone Status after Hip Fracture. Acta Med Biol **54**(3)：93-98, 2006.
12) Sakuma M et al：Incidence and outcome of osteoporotic fractures in 2004 in Sado City, Niigata Prefecture, Japan. J Bone Miner Metab **26**：373-378, 2008.
13) Sakuma M et al：Serum 25-hydorxy vitamin D status in hip and spine-fracture patients in Japan. J Orthop Sci **16**：418-423, 2011.
14) Oyen J et al：Vitamin D inadequacy is associated with low energy distal radius fractures：A case control study. Bone **48**：1140-1145, 2011.
15) Suzuki T：Low serum 25-OHD levels associated with falls among Japanese. J Bone Miner Res **23**：1309-1317, 2008.
16) Kuroda T：Contributions of 25OHD, comorbidities and bone mass to mortality. Bone **44**：168-172, 2009.
17) Kudo Y et al：Risk factors for falls in community-dwelling patients with Alzeheimer's disease and dementia with Lewy bodies：walking with visuocognitive impairement may cause a fall. Dement Geriatr Cogn Disord **27**：139-146, 2009.
18) Giovannucci E et al：25-hydroxyvitamin D and risk of myocardial infarction in men. Arch Intern Med **168**：1174-1180, 2008.
19) Miller JW：Vitamin D and cognitive function in older adults. Neurology **74**：13-15, 2010.
20) Chaganiti RK et al：Association of 25-hydroxyvitamin D with prevalent osteoarthritis of hip in elderly men. Arthritis Rheum **62**：511-514, 2010.
21) Milligan GB and Licata AL：Taking vitamin D with the largest men improves absorption and results in higher serum levels of 25-hydroxyvitamin D. J Bone Miner Res **25**：928-930, 2010.
22) Colston KW：Vitamin D and breast cancer risk. Best Prac Res Clin Endocrinol Metab **22**：587-599, 2008.
23) Bishoff-Ferrari HA et al：Effect of vitamin D on falls：a meta-analysis. JAMA **291**：1999-2006, 2004.
24) Chapuy MC et al：Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med **327**：1637-1642, 1992.
25) Dawson-Hughes B et al：Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med **37**：670-676, 1997.
26) Tilyard MW et al：Treatment of postmenopausal osteoporosis with calcitrol or calcium. N Engl J Med **326**：357-362, 1992.
27) Tanizawa T et al：Treatment with active vitamin D metabolism and concurrent treatment in the prevention of hip fractures：a retrospective study. Osteoporosis Int **9**：163-170, 1999.
28) Cranney A et al：Summary of meta-analysis of therapies for postmenopausal osteoporosis. Endocr Rev **23**：570-578, 2002.
29) Gallagher JC et al：Combination treatment with estrogen and calcitriol in the prevention of age-realted bone loss. J Clin Endocrinol Metab **86**：3618-3628, 2001.
30) Orimo H et al：Effect of 1 α-hydroxy vitamin D3 on lumbar bone mineral density and verte-

bral fractures in patients with postmenopausal osteoporosis. Calcif Tissue Int **54**：370-376, 1994.
31) Papadimiropoulos E et al：The osteoporosis methodology group and osteoporosis research advisory group：meta-analysis of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev **23**：560-569, 2002.
32) Cao Y et al：1Alpha, 25-dihydroxy-2beta(3-hydroxypropoxy)vitamin D3(ED-71) suppressed callus remodeling but did not interfere with fracture healing in rat femora. Bone **40**：132-139, 2007.
33) Shiraki M et al：Design of a pragmatic approach to evaluate the effectiveness of concurrent treatment for prevention of osteoporotic fractures. J Bone Miner Metab **29**：37-43, 2011.

（執筆者連絡先） 遠藤直人 〒951-8510 新潟県新潟市中央区旭町通一番町757 新潟大学大学院医歯学総合研究科機能再建医学講座整形外科学分野（医学部整形外科学教室）

further training of doctors and education among population on osteoporosis is required.

Disclosure of Interest: None declared.

P517

EVIDENCE FOR AN ASSOCIATION BETWEEN SEASONAL FLUCTUATION OF 25(OH)D AND SERUM C-TELOPEPTIDE (CTX): PRELIMINARY EVIDENCE FROM THE D-FINES STUDY

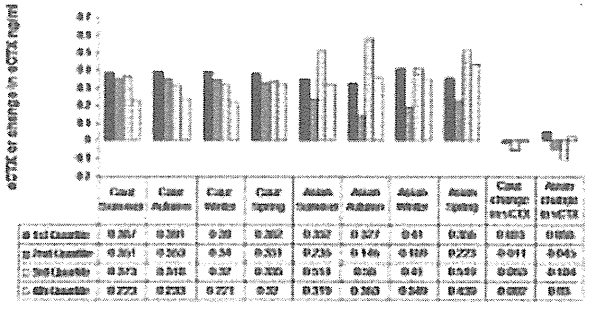
Andrea Darling[1], Fatma Gossiel[2], Rosemary Hannon[2], Debra Skene[1], Jacqueline Berry[3], Richard Eastell[2], Susan Lanham-New[1]

[1]University of Surrey, Faculty of Health and Medical Sciences, Guildford, Surrey, GB, [2]University of Sheffield, Academic Unit of Bone Metabolism, Sheffield, GB, [3]University of Manchester, Vitamin D Research Group, Manchester, GB

Objectives: This analysis assessed whether there is a difference in bone resorption by degree of seasonal change in 25(OH)D and whether this varies by ethnicity.

Materials/Methods: In the recent D-FINES study (2006–2007) a subset of 65 subjects from the 293 participants (South Asian (*n* 30) and Caucasian (*n* 35)) had blood taken in four seasons to assess 25(OH)D and serum c-telopeptide (sCTX). sCTX was measured using an electrochemiluminescent immunoassay (Roche cobas e411). Seasonal fluctuation of 25(OH)D was assessed by calculating the difference between the winter (nadir) and summer (peak) 25(OH)D. This variable was then split into quartiles within ethnicity.

Results: ANCOVA was run with absolute summer and winter 25(OH)D status, age, BMI, socioeconomic status, physical activity, and dietary calcium as covariates. In the Asian group there was no clear trend between degree of seasonal fluctuation and absolute sCTX. Indeed, for absolute sCTX, only the autumn data was statistically significant (F=5.93; p=0.01). No data were significant for change in summer to winter sCTX despite a trend in both ethnic groups for lower sCTX in the middle quartiles relative to the highest and lowest. Last, in Caucasians, there was a nonstatistically significant (p>0.05) inverse trend between cycling of 25(OH)D and absolute serum C-telopeptide levels.



Conclusions: These data suggest lower bone resorption in all seasons in Caucasians with increased cycling, and a reduction in sCTX between summer and winter in both ethnic groups in the middle quartile relative to the other quartiles. As the values were covariate adjusted, these trends are not likely to be due to other variables.

Acknowledgement: The D-FINES study was funded by the UK Food Standards Agency (N05064). All views are those of the authors alone.

Disclosure of Interest: None declared.

P518

EFFECTS OF CALCITONIN TREATMENT IN PATIENTS WITH OSTEOPOROSIS WHO DEVELOPED ACUTE LOW BACK PAIN DUE TO A NEW VERTEBRAL FRACTURE

Shinya Tanaka[4], Naoto Endo[1,2], Keiji Fujino[3]

[1]The Japanese Society for Muscloskeletal Rehabilitation and The Japanese Clinical Orthopaedic Association, The Ad Hoc Committee for Clinical Trial of Osteoporotic Pain, Tokyo, JP, [2]Niigata University, Orthopaedic Surgery, Niigata, JP, [3]Fujino Orthopaedic Clinic, Tokyo, JP, [4]Saitama Medical University, Orthopaedic Surgery, Iruma-gun, Saitama, JP

Objectives: Many elderly subjects have become bedridden or self-confined due to a vertebral fracture associated with osteoporosis. This study was performed to determine whether calcitonin treatment is effective for achieving early ambulation and preventing confinement to bed, in comparison with oral treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), in patients with osteoporosis who developed acute low back pain after suffering a new vertebral fracture.

Materials/Methods: This was a multicenter, open-label, randomized study including female patients aged 65 years and over with primary osteoporosis who developed low back pain after suffering a new fragile fracture of the vertebrae. They were randomized either to receive intramuscular injection of calcitonin at 20 IU once weekly or oral treatment with NSAIDs. The study endpoints comprised the degree of low back pain assessed using the visual analog scale (VAS) and patients' quality of life (QOL) rated using the Roland Morris Questionnaire (RDQ) and the Japan Questionnaire for Osteoporotic Pain (JQ22).

Results: The low back pain according to VAS assessment and QOL assessed using RDQ and JQ22 improved in both patients treated with calcitonin and those receiving oral NSAIDs at the end of Week 4 of study treatment. The assessment results were superior in these variables for the calcitonin group in comparison with the NSAIDs group,

J Orthop Sci (2010) 15:737–745
DOI 10.1007/s00776-010-1543-4

JOURNAL OF
ORTHOPAEDIC SCIENCE

Original article

Nationwide one-decade survey of hip fractures in Japan

Hiroshi Hagino[1], Keizo Sakamoto[2], Atsushi Harada[3], Toshitaka Nakamura[4], Yoshiteru Mutoh[5], Satoshi Mori[6], Naoto Endo[7], Tetsuo Nakano[8], Eiji Itoi[9], Kiyoshi Kita[10], Noriaki Yamamoto[11], Kiyoshi Aoyagi[12], and Kaoru Yamazaki[13] for the Committee on Osteoporosis of The Japanese Orthopaedic Association

[1]School of Health Science, Tottori University, 86 Nishi-Cho, Yonago, Tottori 683-8503, Japan
[2]Department of Orthopaedic Surgery, Showa University School of Medicine, Tokyo, Japan
[3]Department of Advanced and Restorative Medicine, National Center for Geriatrics and Gerontology, Aichi, Japan
[4]Department of Orthopaedic Surgery, School of Medicine, University of Occupational and Environmental Health, Fukuoka, Japan
[5]Department of Physical and Health Education, Graduate School of Education, The University of Tokyo, Tokyo, Japan
[6]Department of Bone and Joint Surgery, Seirei Hamamatsu General Hospital, Hamamatsu, Japan
[7]Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[8]Department of Orthopaedic Surgery, Tamana Central Hospital, Tamana, Kumamoto, Japan
[9]Department of Orthopaedic Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan
[10]Kita Orthopaedic Clinic, Kobe, Japan
[11]Department of Orthopaedic Surgery, Niigata Rehabilitation Hospital, Niigata, Japan
[12]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[13]Department of Orthopedic Surgery, Iwata City Hospital, Iwata, Japan

Abstract

Background. To elucidate the characteristics of hip fractures and the current status of their treatment in Japan, the Japanese Orthopaedic Association (JOA) conducted a nationwide hip fracture survey from 1998 to the present. The aim of the current report was to present the changes in patient distribution by age and fracture type, cause of fracture, treatment selection, and duration of hospitalization for a study period of one decade.

Methods. A tally of all hip fractures that occurred in patients between 2001 and 2008 was conducted in JOA-authorized hospitals and in Japanese Clinical Orthopaedic Association (JCOA) hospitals. Registration forms were sent to these hospitals each year, and registration was performed based on their hospital records.

Results. The mean response rate was 51.8%, and the total number of patients aged ≥35 with new hip fractures between 2001 and 2008 was 402 760. A drastic increase in the number of patients, especially those aged ≥90 was observed over the course of the decade. More trochanteric fractures occurred than neck fractures during the observational period; however, the neck/trochanter ratio increased over time. Simple falls were the most common cause of fracture. About 94% patients were treated surgically with about a 5-day presurgical hospital stay, and the mean hospitalization period was 40.7 days in 2008.

Conclusions. This one-decade survey demonstrated a drastic increase in the number of patients over the course of the decade in Japan. Appropriate treatment and prevention of hip fractures, including the treatment of osteoporosis and more effective interventions for preventing falls, are important issues to address to reduce the burden of this fracture.

Offprint requests to: H. Hagino
Received: March 29, 2010 / Accepted: August 5, 2010

Introduction

Hip fractures are not only the most significant osteoporotic fracture in terms of health outcome or quality of life, they also account for a substantial proportion of health service expenses. As a result of the aging population in most industrialized countries, the burden of this fracture type on our health care systems is increasing, and the absolute number of hip fractures is expected to rise significantly over the next few decades.

A growing number of epidemiological surveys have shown a recent exponential increase in the number of hip fractures among various ethnic groups. It is well known that the incidence of hip fractures in northern Europe or North America is substantially higher than that in Asian counties; however, whereas this incidence was once increasing in Europe and America, it has now plateaued or is decreasing.[1,2] On the contrary, it has been reported that hip fracture incidence increased steadily from 1986 to 2006 in Japan,[3] which agreed with most other studies from Asia. It is estimated that the annual number of hip fractures worldwide will be 2.6 million by the year 2025, and the number of hip fractures could range between 7.3 and 21.3 million by 2050.[4] Although Europe and North America account for about one-half of all hip fractures among elderly people today, this proportion will fall to around one-fourth in 2050,

Table 1. Number of institutions and response rates

Survey year	JOA-authorized hospitals	JCOA hospitals	Total	Response rate (%)
1998[a]	2270	1529	3799	48.4
1999[a]	2264	1430	3694	55.1
2000[a]	2312	1512	3824	47.0
2001	2291	1493	3784	53.0
2002	2276	1466	3742	53.6
2003	2252	1347	3599	52.1
2004	2264	1258	3522	51.3
2005	2229	1224	3453	48.3
2006	2201	1167	3368	48.9
2007	2031	1218	3249	51.8
2008	2016	1104	3120	55.4

JOA, Japanese Orthopaedic Association; JCOA, Japanese Clinical Orthopaedic Association
[a] Data are from reference 9

by which time steep increases will be observed throughout Asia and Latin America.[5] Therefore, the medical and socioeconomic burden of hip fractures will be growing rapidly in Asian countries.

Japan is the country with the longest life expectancy in the world. The average life expectancy at birth for Japanese individuals has steadily increased, reaching 78.56 years for men and 85.52 years for women in 2005. As a result, the population structure in Japan has changed dramatically over the past decade. The proportion of the population aged ≥65 years increased from 17.5% in 2000 to 22.3% in 2008, and the proportion aged ≥75 years grew from 7.1% to 10.5%.[6] As a result of these changes, Japan's population now contains more elderly individuals than any other developed countries, and the hip fracture burden will therefore be more serious in Japan than in any other country in the near future. In 2005, the life expectancy for 50-year-old men was 29.26 years and that for women was 35.94 years, and the residual lifetime risk of hip fracture for individuals 50 years of age in Japan was estimated to be 5.6% for men and 20.0% for women.[3] This compares to 10.7% and 22.9% in Sweden and 3.1% and 11.4% in the United Kingdom, for men and women, respectively.[7,8] Although the incidence of hip fracture in Japan is lower than that in Sweden,[3] the longer average life-span has elevated the residual lifetime fracture risk for individuals 50 years of age.

To elucidate the characteristics of hip fractures and the current status of their treatment in Japan, the Japanese Orthopaedic Association (JOA) conducted a nationwide hip fracture survey from 1998 to the present. We previously reported the survey results obtained between 1998 and 2000.[9] The aim of the current report was to present additional results from 2001 to 2008, thus describing for a study period of one decade the change in patient distribution by age and fracture type, cause of fracture, treatment selection, and duration of hospitalization.

Patients and methods

Data collection

A tally of all hip fractures that occurred in patients between 2001 and 2008 was conducted in JOA-authorized hospitals and in Japanese Clinical Orthopaedic Association (JCOA) hospitals. There were 2291 JOA-authorized hospitals and 1493 JCOA hospitals in 2001, and the number decreased thereafter (Table 1).

Inclusion criteria were femoral neck and trochanteric fractures in patients aged ≥35 years and treated in JOA-authorized or JCOA hospitals. Pathological fractures due to neoplasm or infection and removal of implants were excluded. Cases of refracture were included, but cases of reoperation due to delayed union or nonunion were excluded. Registration forms were sent to these hospitals by mail each year, and registration was performed by the hospital staff (including orthopedists) based on their hospital records. Registration information included name (initials), sex, date of birth, date of fracture, date of first hospital visit, fracture site, fracture type, fracture location, cause of injury, treatment, and duration of hospitalization. From 2005 onward, the initials and date of birth were omitted from the registration information for the purpose of protecting personal information. Therefore, duplication of cases and refracture were checked based on patient initials, date of birth, and prefecture before 2005 and by fracture date, age, sex, and prefecture from 2005 to 2008.

Causes of injury were divided into six categories: "in bed," "simple fall," "fall on stairs," "traffic accident," "not remembered," and "unknown." The term "in bed"

Table 2. Registered patients ≥35 years old with a hip fracture

Survey	No. of patients			Fracture site	
	Male	Female	Total	Right	Left
1998[a]	7 761	28 275	36 226	17 552	18 379
1999[a]	8 556	31 253	40 069	19 375	20 253
2000[a]	7 351	26 889	34 452	16 786	17 458
2001	9 193	35 097	44 469	21 650	22 565
2002	9 547	35 840	45 604	22 185	23 144
2003	9 414	35 189	44 807	21 731	22 790
2004	9 499	36 134	45 835	22 001	23 551
2005	9 644	36 397	46 145	22 287	23 376
2006	10 646	40 087	50 846	24 518	25 738
2007	11 937	44 787	56 816	27 409	28 950
2008	14 334	53 783	68 238	32 795	34 805
Total	84 214	317 314	402 760	194 576	204 919

Values are the number of patients
[a]Data are from reference 9

indicates a fracture that occurred when lying in bed, "simple fall" describes falling from a standing height or from bed, "not remembered" indicates that the patient did not remember the injury, and "unknown" denotes that the information could not be obtained from patients because of some difficulty, such as dementia. We identified "care fractures" as those that occurred during activities involving care of bed-ridden patients (e.g., during diaper changing and bed baths) and included them in the "in bed" category.

The duration of hospitalization was calculated based on the hospital where the patients were treated just after their injury. Surgical day for the first surgery (e.g., osteosynthesis, arthroplasty) was surveyed from 2003 to 2008, and the duration of hospitalization before surgery was calculated.

Statistical methods

Significant differences between two groups were tested with Wilcoxon tests for paired values (for the number of patients fractured on the right or left side during each year) and Mann-Whitney tests for unpaired values. Patient proportions between groups were compared using the chi-squared test. Seasonal variations were tested with the Friedman test. Approval was obtained from the ethics committees of the JOA, Tottori University, and each participating hospital. Statistical analysis was performed using SPSS (SPSS II for Windows Version 11.0.1J; SPSS Japan, Tokyo, Japan); and $P < 0.05$ was considered statistically significant. Patient data obtained between 1998 and 2000, which we previously reported,[9] was included in this analysis.

Results

Response rates and number of patients

Response rates ranged from 48.3% to 55.4% (mean 51.8%) (Table 1). The total number of patients aged ≥ 35 years with new hip fractures between 2001 and 2008 was 402 760 (84 214 men, 317 314 women, sex not indicated 1232 cases) (Table 2). The number of women was 3.8 times that of men.

Fractures occurred on the right in 194 576 patients and on the left in 204 919 patients (fracture site was not indicated in 3265 cases) (Table 2). More left hips were fractured than right in all survey years, and the difference was statistically significant ($P < 0.02$, Wilcoxon test).

Age-specific and sex-specific patient totals

Age-specific and sex-specific patient totals were calculated for each survey year. Patient numbers correlated with higher age and peaked in the 85- to 89-year-old group for both sexes (Fig. 1). Patients in the 80- to 89-year-old age group accounted for about half of the total number of patients. However, increases in patient numbers over time (from 1998 to 2008) were more prominent for ages ≥90 years for both sexes. The numbers of female patients were 6531, 6241, and 2766 in 1998 for the age groups 80–84, 85–89, and 90–94 years, respectively; they were 12 147, 13 180, and 8358, for these same groups in 2008. The ratios of fracture numbers in 2008 to those in 1998 are 1.90, 2.11, and 3.04, respectively. There were 1413 women and 202 men aged ≥100 years with hip fractures during the period 2001–2008.

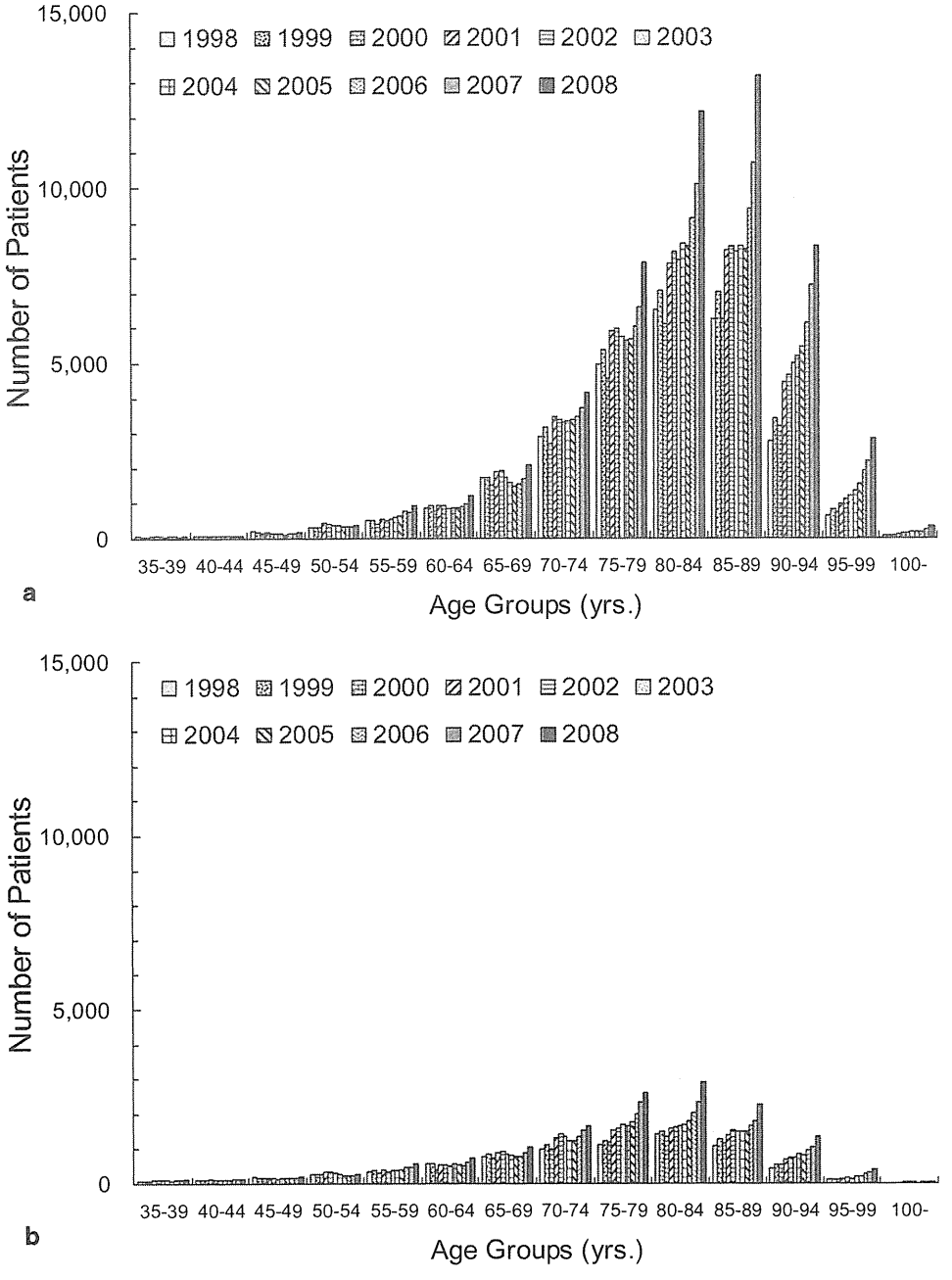


Fig. 1. Age-specific annual numbers of patients with hip fractures. **a** Women. **b** Men. The number increased with age and peaked at age 85–89 years for both sexes. Patients in the 80- to 89-year-old age group accounted for about one-half of the total number of patients; but for both sexes the increases were more prominent for those aged ≥90 years

Fracture type

The survey found 182 576 neck fractures and 216 788 trochanteric fractures (3396 unclassified fractures) during the observational period from 2001 to 2008. The change over time in the prevalence of both fracture types is shown in Fig. 2. More trochanteric fractures occurred than neck fractures during the observational period; however, the neck/trochanter ratio increased over time.

Refractures

Patients with refracture at either the opposite or same side of the first fracture side were determined from 2001 to 2004 based on patients' initials and dates of birth (Table 3). During the 1-year observational period 1916 patients (197 men, 1719 women) suffered refracture (Table 3). Initial fractures occurred on the right side in 981 patients and on the left side in 908 patients (fracture side not indicated in 27 cases); 883 of these were neck

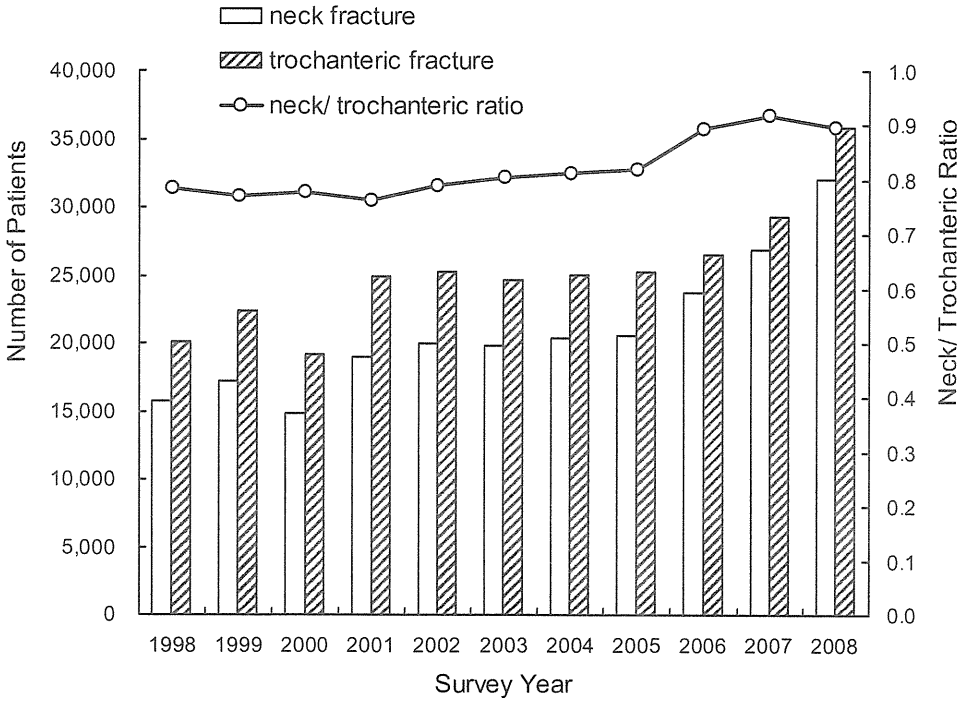


Fig. 2. Fracture type-specific annual numbers of patients with hip fractures. More trochanteric than neck fractures occurred during the observational period, although the neck/trochanter ratio increased over time

Table 3. Patients with refracture

Parameter	2001	2002	2003	2004	Total
Sex (no.)					
Men	49	42	51	55	197
Women	430	431	429	429	1719
First fracture					
Fracture site (no.)					
Right	244	248	244	245	981
Left	228	220	231	229	908
Fracture type					
Neck	239	215	225	204	883
Trochanteric	236	254	244	267	1001
Second fracture of the same type	70.1%	64.1%	66.3%	69.0%	67.4%

fractures, and 1001 were trochanteric fractures (fracture type not indicated in 32 cases). Refractures were of the same type as the initial fractures in 67.4% of cases and on the same side in 2.3% of cases.

Fracture causes

Fractures were due to a simple fall in more than two-thirds of men and four-fifths of women (Table 4). In patients aged ≥90 years, a simple fall was the cause in more than 84% of cases. "Care fractures" were identified in 0.2% of the total number of patients.

Altogether, 75% (277 657) of patients sustained fractures indoors, and 25% (93 679) sustained them outdoors (the site of the injury was not indicated in 31 424 cases). Patients aged ≥90 years sustained their fractures indoors 87.9% of the time, whereas this was the case for only 71.8% of patients <90 years of age, a statistically significant difference ($P < 0.001$, chi-squared test). Comparing sexes, 78.7% of women and 60.3% of men suffered fractured indoors, again a difference that was statistically significant ($P < 0.001$, chi-squared test).

Monthly variation

The total number of patients per month was the highest in January in all survey years from 1998 to 2008. It was the lowest in June in all survey years except 2000, when the lowest number was observed in July (Fig. 3). This monthly variation was statistically significant ($P < 0.01$, Friedman test).

Table 4. Cause of hip fractures

Cause	Total	Men	Women	Age < 90 years	Age ≥ 90 years
Simple fall	305 473 (77.7%)	56 950 (69.1%)	248 523 (80.1%)	247 634 (76.4%)	57 839 (84.1%)
Traffic accident	32 754 (8.3%)	15 293 (18.5%)	17 461 (5.6%)	30 688 (9.5%)	2 066 (3.0%)
Fall on stairs	21 994 (5.6%)	4 847 (5.9%)	17 147 (5.5%)	19 776 (6.1%)	2 218 (3.2%)
In bed	5 540 (1.4%)	945 (1.1%)	4 595 (1.5%)	4 292 (1.3%)	1 248 (1.8%)
Not remembered	5 294 (1.3%)	816 (1.0%)	4 478 (1.4%)	4 415 (1.4%)	879 (1.3%)
Unknown	21 843 (5.6%)	3 607 (4.4%)	18 236 (5.9%)	17 317 (5.3%)	4 526 (6.6%)
Care fracture[a]	805 (0.2%)	136 (0.2%)	669 (0.2%)	594 (0.2%)	211 (0.3%)

Values are the total number of patients (years 2001–2008)
[a]Those that occurred during the care of bedridden patients, such as when changing a diaper

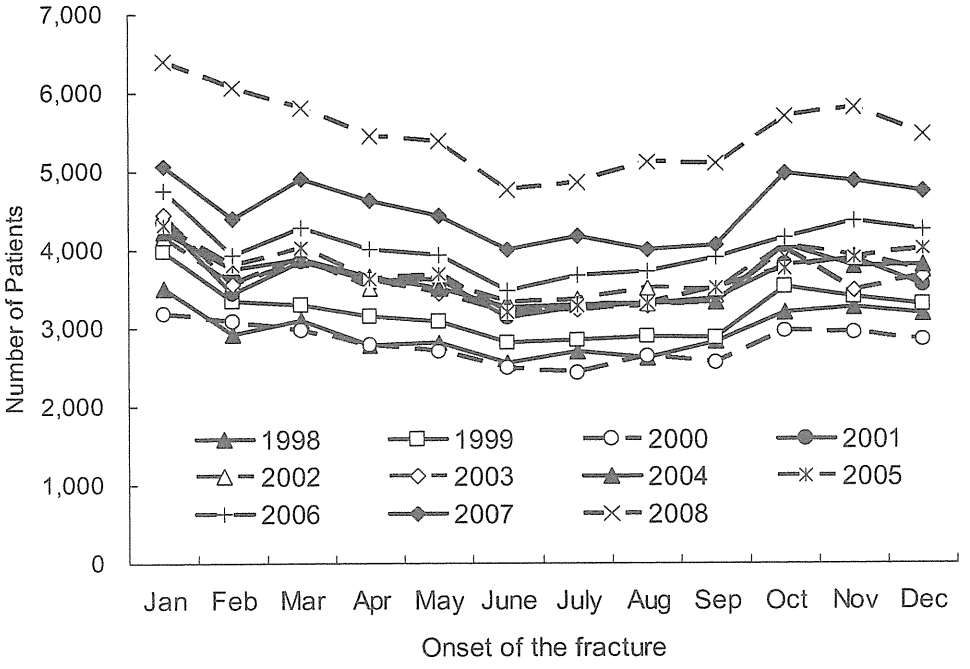


Fig. 3. Monthly variation in the number of patients with hip fractures

Length of stay before surgery or other treatment

More than 90% of patients were treated surgically (Table 5). Among patients with femoral neck fractures, 67.5% were treated with arthroplasty including hemiarthroplasty and total arthroplasty.

The mean length of stay (LOS) before surgery was 5.6 days in 2003, becoming shorter with time over successive observational periods (Table 6). The LOS for neck fractures was longer than that for trochanteric fractures during all survey years ($P < 0.001$ Mann-Whitney). Among patients with neck fractures, the mean LOSs before surgery for patients receiving arthroplasty were 6.5, 6.3, 6.2, 6.1, 6.0, and 5.8 days in 2003, 2004, 2005, 2006, 2007, and 2008, respectively. Those for patients undergoing osteosynthesis were 4.7, 4.6, 4.5, 4.8, 4.2, and 4.3 days, respectively. These differences between fracture types were significant in all survey years ($P < 0.001$ Mann-Whitney). The mean LOSs before surgery among patients aged ≤90 years were 5.7, 5.4, 5.4, 5.2, 5.1, and 4.9 days in 2003, 2004, 2005, 2006, 2007, and 2008, respectively. Those among patients aged ≥90 years were 5.2, 5.1, 4.8, 5.0, 4.8, and 4.7 days, respectively. These differences between age groups were significant in all survey years ($P < 0.001$ Mann-Whitney).

Duration of hospitalization

The mean hospitalization period was 53.4 days in 2001, and it became shorter over successive observational periods (Table 6). There was no significant difference in hospitalization duration between patients with neck fractures and those with trochanteric fractures. The hospitalization period was longer in patients <90 years of age than in those ≥90 years in all survey years ($P < 0.001$ Mann-Whitney).

Table 5. Selected treatment for patients with hip fractures

Treatment	Neck	Trochanter	Total
Conservative	11 151 (6.2%)	11 589 (5.4%)	22 740 (5.8%)
Surgery	167 549 (93.8%)	201 715 (94.6%)	369 264 (94.2%)
Arthroplasty	113 130 (67.5%)	2 276 (1.1%)	115 406 (31.3%)
Osteosynthesis	53 450 (31.9%)	198 316 (98.3%)	251 766 (68.2%)
Not indicated	969 (0.6%)	1 123 (0.6%)	2 092 (0.6%)

Values are the total number of patients (years 2001–2008)

Table 6. Preoperative and hospitalization periods

Survey year	Preoperative period (days)			Hospitalization period (days)		
	Neck fracture	Trochanteric fracture	Total	Neck fracture	Trochanteric fracture	Total
2001	—	—	—	53.2, 46 [31–67]	53.5, 46 [29–69]	53.4, 46 [30–68]
2002	—	—	—	50.2, 43 [28–63]	50.6, 43 [27–65]	50.5, 43 [28–64]
2003	5.9, 5 [3–7]	5.3, 4 [2–7]	5.6, 4 [2–7]	48.4, 41 [27–61]	49.6, 42 [26–64]	49.2, 42 [27–63]
2004	5.4, 4 [2–7]	5.0, 4 [2–6]	5.4, 4 [2–7]	47.0, 40 [26–60]	49.0, 41 [26–63]	48.1, 40 [26–61]
2005	5.3, 4 [2–7]	4.9, 4 [2–6]	5.3, 4 [2–7]	47.4, 40 [26–60]	48.6, 41 [25–63]	48.0, 40 [26–62]
2006	5.2, 4 [2–7]	4.8, 4 [2–6]	5.2, 4 [2–7]	44.7, 38 [24–57]	45.2, 38 [23–59]	44.9, 38 [24–58]
2007	5.4, 4 [2–7]	4.7, 4 [2–6]	5.0, 4 [2–6]	42.0, 35 [22–54]	42.7, 35 [22–56]	42.3, 35 [22–55]
2008	5.3, 4 [2–7]	4.6, 4 [2–6]	4.9, 4 [2–6]	40.6, 33 [21–51]	40.7, 33 [21–53]	40.7, 33 [21–52]

Values are the mean, median, and [25%–75% percentiles]

Discussion

This study evaluated the relation of hip fracture incidence to age and fracture type, cause of fracture, treatment selection, length of stay before surgery, and duration of hospitalization. The survey showed a drastic increase in number of patients, especially those aged ≥90 years, over the course of one decade. Simple falls were the most common cause of fracture, and about 94% patients were treated surgically with about a 5-day presurgical hospital stay.

Studies in Japan have indicated that hip fracture incidence has been increasing up to the present time.[3,10] A recent study showed a slight decline in the incidence of hip fracture; however, it is limited in some age groups.[11] The current study demonstrated a drastic increase in the number of patients over age 80 years between 1998 and 2008, with numbers in 2008 eclipsing those in 1998 by factors of 1.90, 2.11, and 3.04 for the age ranges 80–84, 85–89, and 90–94 years, respectively. The number of patients ≥100 years of age with hip fractures quadrupled from 1998 to 2008. These increases are much higher than those seen in the remainder of the Japanese population from 1998 to 2008, where ratios were 1.64, 1.56, and 1.63 for the age groups 80–84, 85–89, and 90–94 years, respectively.[6] The registered number of patients per year in each hospital also increased during the observational period. As the 50% response rate demonstrates, this study does not cover all patients with hip fractures in Japan. Nonetheless, the substantially higher number of patients registered than those expected based on the Japanese population increase is due to the increase in hip fracture incidence in individuals aged ≥ 80 years that we previously reported.[3] The overall decrease in physical activity stemming from a Westernized lifestyle may explain the increase in fracture incidence among Japanese patients. Another explanation may be that more seniors with poor health because of other conditions are being treated, which results in people living longer at a time when their risk of falling is quite high.[3]

The most serious social and economic concern facing our health care system is the rapid rise in the number of patients aged ≥90 years. It has been estimated that these patients will account for half of the total number of hip fractures within the next two decades, by which time the total number of hip fractures sustained per year will be about 300 000, approximately double that in 2008. Establishing effective measures to support elderly patients with hip fractures is one of the more urgent issues in our society.

The incidence of femoral neck fractures is higher than that of trochanteric fractures in northern European and African populations, whereas femoral neck fractures are less common than trochanteric fractures in Japanese populations.[3,12,13] Because trochanteric fractures have a closer relation with low bone mass than do femoral neck fractures, they occur more frequently in the very

elderly.[14] As a result, we had expected that the increase in hip fractures over the last decade would be marked by a relatively higher number of trochanteric fractures than femoral neck fractures — when in fact the opposite was seen. A recent survey in Sweden showed that the neck/trochanteric fracture incidence ratio had leveled off.[15] Although the reason for these trends is uncertain, the neck/trochanteric fracture ratio in Japan might be approaching values observed in northern European populations.

In this study, more left-sided fractures than right-sided fractures were observed. Most patients are right-handed,[16] and it is speculated that falls to the left side exert more impact on the proximal femur than falls to the right owing to poor protection by the nondominant hand.

It is well known that the risk of further hip fractures increases after an initial fracture,[17] so we evaluated second hip fractures occurring during the same year. Although a 1-year observation is insufficient to elucidate the risk of second fracture, about one-fourth of all subsequent fractures occur within 1year after a first fracture.[18] In this study, the primary hip fractures in patients with a refracture occurred more on the right side than the left, implying that patients with their first hip fracture on the right side have a higher risk of sustaining a second hip fracture than those in whom the primary fracture occurred on the left side.

In this study, a peak in the number of patients with hip fractures was seen in January. A recent study indicated that incidence rates of fragility fractures were highest in winter and lowest in summer.[19] Significant seasonality and an association of monthly hip fracture admission rates with ambient temperature were observed in both sexes.[20] Several explanations have been proposed, including low blood pressure, reduced vitamin D production, and heavier clothing during cold weather months. Because the present study found simple falls to be the most common cause of hip fractures and more fractures occurred indoors than outdoors, reducing the risk of indoor falling during the winter is a significant point to be emphasized for the prevention of hip fractures.

This study was the first to report on the length of stay before surgery throughout Japan. The average length was about 5 days, which is substantially longer than the duration reported by other countries.[21–23] Although it does not seem that high-quality evidence has been established up to this point, early surgery (within 2 days) is recommended to minimize postsurgical hospitalization time and complications.[24,25] We have to make every endeavor to shorten the length of hospital stays before surgery.

This study showed that over the course of one decade the duration of hospitalization after surgery became shorter with time, although even as of 2008 it remained much longer than that reported in Europe or North America. The Japanese health care system and insurance programs might contribute to this fact. In a recent study performed in the United States and Japan, shorter lengths of stay after surgery did not predict better survival across the two countries.[23] Another study demonstrated that reducing the length of stay in initial acute care hospitals may be just a method of shifting costs to subsequent care services and is unlikely to bring overall cost saving to the Japanese health care system.[26] It is necessary, therefore, to develop strategies that move beyond simple approaches and efficiently and effectively reduce the hospital stay of hip-fractured patients.

There are several limitations to this study. First, the response rate of 50% was somewhat low. Second, although the survey was conducted in hospitals authorized by the JOA and JCOA, surgery for hip fractures is performed not only in these hospitals but also at nonaffiliated hospitals. However, the large number of patients surveyed in this study for more than one decade may compensate for any such bias. Third, the initials and date of birth were omitted from the registration information from 2005 onward; therefore, patients with refracture were not evaluated thereafter. This may have affected the result, although patients moved from other hospitals were checked by each hospital and most patients analyzed for this study were those hospitalized just after the injury.

Conclusion

This one-decade survey studied more than 400 000 patients with hip fractures and demonstrated a drastic increase in the number of patients over the course of the decade, especially in the group aged ≥90 years. Appropriate treatment and prevention of hip fractures, including the treatment of osteoporosis and more effective interventions to prevent falls, are important issues to address to reduce the burden of this fracture.

Acknowledgments. The authors sincerely thank all staff members at the hospitals cooperating in this study. This study was partially supported by a grant-in-aid from the Ministry of Health, Labor, and Welfare of Japan (grants H18-Choujyu Ippann-036 and Choujyu Iryou Kenkyu 21-Shi16).

References

1. Abrahamsen B, Vestergaard P. Declining incidence of hip fractures and the extent of use of anti-osteoporotic therapy in Denmark 1997–2006. Osteoporos Int 2010;21:373–80.
2. Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, Bancej C, et al. Trends in hip fracture rates in Canada. JAMA 2009;302: 883–9.

3. Hagino H, Furukawa K, Fujiwara S, Okano T, Katagiri H, Yamamoto K, et al. Recent trends in the incidence and lifetime risk of hip fracture in Tottori, Japan. Osteoporos Int 2009;20:543–8.
4. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. Osteoporos Int 1997;7:407–13.
5. Cooper C, Campion G, Melton LJ 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporos Int 1992;2:285–9.
6. Ministry of Health Law. Statistics & Other Data. 2009.
7. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int 2000;11:669–4.
8. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. Osteoporos Int 2005;16(suppl 2):S3–7.
9. Committee for Osteoporosis Treatment, The Japanese Orthopaedic Association. Nationwide survey of hip fractures in Japan. J Orthop Sci 2004;9:1–5.
10. Morita Y, Endo N, Iga T, Tokunaga K, Ohkawa Y. The incidence of cervical and trochanteric fractures of the proximal femur in 1999 in Niigata Prefecture, Japan. J Bone Miner Metab 2002;20:311–8.
11. Orimo H, Yaegashi Y, Onoda T, Fukushima Y, Hosoi T, Sakata K. Hip fracture incidence in Japan: estimates of new patients in 2007 and 20-year trends. Arch Osteoporos 2009;4:71–7.
12. Lonnroos E, Kautiainen H, Karppi P, Huusko T, Hartikainen S, Kiviranta I, et al. Increased incidence of hip fractures: a population based-study in Finland. Bone 2006;39:623–7.
13. Bjorgul K, Reikeras O. Incidence of hip fracture in southeastern Norway: a study of 1,730 cervical and trochanteric fractures. Int Orthop 2007;31:665–9.
14. Mautalen CA, Vega EM, Einhorn TA. Are the etiologies of cervical and trochanteric hip fractures different? Bone 1996;18: 133S–7S.
15. Lofman O, Berglund K, Larsson L, Toss G. Changes in hip fracture epidemiology: redistribution between ages, genders and fracture types. Osteoporos Int 2002;13:18–25.
16. Hagino H, Fujiwara S, Nakashima E, Nanjo Y, Teshima R. Case-control study of risk factors for fractures of the distal radius and proximal humerus among the Japanese population. Osteoporos Int 2004;15:226–30.
17. Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P. Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977–2001. J Bone Miner Res 2009;24:1299–307.
18. Van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis 2009;68:99–102.
19. Bischoff-Ferrari HA, Orav JE, Barrett JA, Baron JA. Effect of seasonality and weather on fracture risk in individuals 65 years and older. Osteoporos Int 2007;18:1225–33.
20. Lin HC, Xiraxagar S. Seasonality of hip fractures and estimates of season-attributable effects: a multivariate ARIMA analysis of population-based data. Osteoporos Int 2006;17:795–806.
21. Vidal EI, Moreira-Filho DC, Coeli CM, Camargo KR Jr, Fukushima FB, Blais R. Hip fracture in the elderly: does counting time from fracture to surgery or from hospital admission to surgery matter when studying in-hospital mortality? Osteoporos Int 2009;20:723–9.
22. Verbeek DO, Ponsen KJ, Goslings JC, Heetveld MJ. Effect of surgical delay on outcome in hip fracture patients: a retrospective multivariate analysis of 192 patients. Int Orthop 2008;32:13–8.
23. Kondo A, Zierler BK, Isokawa Y, Hagino H, Ito Y, Richerson M. Comparison of lengths of hospital stay after surgery and mortality in elderly hip fracture patients between Japan and the United States: the relationship between the lengths of hospital stay after surgery and mortality. Disabil Rehabil 2010;32: 826–35.
24. Majumdar SR, Beaupre LA, Johnston DW, Dick DA, Cinats JG, Jiang HX. Lack of association between mortality and timing of surgical fixation in elderly patients with hip fracture: results of a retrospective population-based cohort study. Med Care 2006;44:552–9.
25. Rae HC, Harris IA, McEvoy L, Todorova T. Delay to surgery and mortality after hip fracture. ANZ J Surg 2007;77:889–91.
26. Kondo A, Zierler BK, Isokawa Y, Hagino H, Ito Y. Comparison of outcomes and costs after hip fracture surgery in three hospitals that have different care systems in Japan. Health Policy 2009;91: 204–10.

J Bone Miner Metab (2011) 29:37–43
DOI 10.1007/s00774-010-0188-x

ORIGINAL ARTICLE

Design of a pragmatic approach to evaluate the effectiveness of concurrent treatment for the prevention of osteoporotic fractures

Rationale, aims and organization of a Japanese Osteoporosis Intervention Trial (JOINT) initiated by the Research Group of Adequate Treatment of Osteoporosis (A-TOP)

Masataka Shiraki · Tatsuhiko Kuroda · Nobuaki Miyakawa · Naohito Fujinawa · Kazumasa Tanzawa · Akiko Ishizuka · Shiro Tanaka · Yukari Tanaka · Takayuki Hosoi · Eiji Itoi · Shigeto Morimoto · Akira Itabashi · Toshitsugu Sugimoto · Toshihiko Yamashita · Itsuo Gorai · Satoshi Mori · Hideaki Kishimoto · Hideki Mizunuma · Naoto Endo · Yoshiki Nishizawa · Kunio Takaoka · Yasuo Ohashi · Hiroaki Ohta · Masao Fukunaga · Toshitaka Nakamura · Hajime Orimo

Received: 27 November 2009 / Accepted: 23 March 2010 / Published online: 13 May 2010

Abstract The aim of osteoporosis treatment is to prevent future fractures. Although concurrent treatment has been used very frequently for osteoporosis in clinical practice, there are no data on accurate and verified effectiveness of concurrent treatment for fracture prevention in patients with osteoporosis. To clarify the clinical usefulness of concurrent treatment, the Japan Osteoporosis Society has authorized the establishment of the A-TOP (Adequate Treatment of Osteoporosis) research group. The objective of this research is to establish a design for a clinical trial to prove whether concurrent treatment using both alfacalcidol (1-alpha-hydroxycholecalciferol) and alendronate is more effective as compared to treatment using alendronate alone

For the A-TOP (Adequate Treatment of Osteoporosis) Research Group.

M. Shiraki (✉)
Department of Internal Medicine, Research Institute and Practice for Involutional Diseases, 1610-1 Meisei, Misato, Azumino, Nagano 399-8101, Japan
e-mail: ripid@fc4.so-net.ne.jp

T. Kuroda · N. Miyakawa
Public Health Research Foundation, Tokyo, Japan

N. Fujinawa
I'cros Co., Ltd., Tokyo, Japan

K. Tanzawa
ING Corporation, Tokyo, Japan

A. Ishizuka
Japan Clinical Research Support Unit, Tokyo, Japan

S. Tanaka
Division of Clinical Trial Design and Management, Translational Research Center, Kyoto University, Kyoto, Japan

Y. Tanaka
Department of Epidemiology and Biostatistics, School of Health Sciences and Nursing, The University of Tokyo, Tokyo, Japan

T. Hosoi
Department of Advanced Medicine, National Center for Geriatrics and Gerontology, Aichi, Japan

E. Itoi
Department of Orthopaedic Surgery, Tohoku University School of Medicine, Sendai, Japan

S. Morimoto
Geriatric Medicine, Kanazawa Medical University, Ishikawa, Japan

A. Itabashi
Saitama Center for Bone Research, Kubojima Clinic, Saitama, Japan

T. Sugimoto
Department of Endocrinology and Metabolism, Faculty of Medicine, Shimane University, Shimane, Japan

T. Yamashita
Department of Orthopaedic Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan

I. Gorai
Department of Obstetrics and Gynecology, International University of Health and Welfare Atami Hospital, Shizuoka, Japan

S. Mori
Bone and Joint Surgery, Seirei Hamamatsu General Hospital, Shizuoka, Japan

in terms of fracture prevention. The present study was named JOINT (Japanese Osteoporosis Intervention Trial) and is based on a method using national, prospective, randomized, open-labeled, blinded endpoints focusing on postmenopausal osteoporosis with a high risk for fracture. The patients were mainly selected by practitioners and allocated randomly by a central registration system into two groups, of which one received 5 mg/day of alendronate alone, and the other received 1 μg/day of 1-alpha-hydroxycholecalciferol (alfacalcidol) in addition to the alendronate. The endpoints focused primarily on fracture prevention, and the patients' quality of life (QOL) and change in body height, as well as adherence and the adverse events of the treatments were evaluated secondarily. To obtain sufficient statistical power in the events during a 2-year observation period, the patients who are expected to have higher risk were selected to participate in this study, and it was decided that the final plan would involve 890 patients per group (two-sided alpha = 0.05, power = 0.8). Data collection began in November 2003. Correspondence regarding the registration of the investigator and the progress of the study was conducted through a web system from the Public Health Research Foundation to practitioners.

Keywords Alendronate · Alfacalcidol · Concurrent treatment · Fracture prevention · Osteoporosis

Introduction

Osteoporosis, which is characterized by compromised bone strength and increased susceptibility to fractures, which lead to deterioration in the QOL and increased mortality, is a national burden on an aging society [1, 2]. However, recent studies indicate that treatment with a parathyroid hormone, bisphosphonates or a selective estrogen receptor modulator (SERM) [3–9] may decrease the risk of fractures in patients with osteoporosis.

Although bisphosphonate treatment currently represents the most powerful form of treatment available for fracture prevention in osteoporotic patients, it has not succeeded in completely preventing osteoporotic fractures [3–5, 7–9]. Therefore, concurrent treatment of osteoporosis has been frequently used by Japanese practitioners without any concrete evidence regarding fracture reduction. Since the concept of evidence-based medicine (EBM) has been introduced to clinical practice since the 1990s [10], the Japan Osteoporosis Society and the Japanese Society of Bone Mineral Research have edited the clinical guideline for treatment of osteoporosis (Chief editor: Hajime Orimo [11]). However, the writers recognized that there was a lack of evidence in the effectiveness of concurrent treatment of osteoporosis. Furthermore, it was expected that the patients who visit clinics have varying degrees of risk of fracture, which may differ from the degree of those who participated in development trials for bisphosphonates. This possibility would make it easier to obtain pragmatic evidence in general clinical practice.

Starting in 2000, the Japan Osteoporosis Society had planned to investigate the effectiveness of treatment of osteoporosis in order to provide evidence to general practitioners. Before constructing evidence, some feasibility studies were required to confirm the consensus in the diagnosis of incident fractures among the researchers and to elucidate the risk of future fractures in the patient population. In addition to these efforts in the field of osteoporosis, the Japanese government also established an

H. Kishimoto
Department of Orthopedic Surgery, San-in Rosai Hospital, Tottori, Japan

H. Mizunuma
Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, Aomori, Japan

N. Endo
Division of Orthopedic Surgery, Niigata University Medical and Dental Hospital, Niigata, Japan

Y. Nishizawa
Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan

K. Takaoka
Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan

Y. Ohashi
Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo, Japan

H. Ohta
Department of Obstetric and Gynecology, Tokyo Women's Medical University, Tokyo, Japan

M. Fukunaga
Department of Nuclear Medicine, Kawasaki Medical School, Okayama, Japan

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

H. Orimo
Health Science University, Yamanashi, Japan

ethical guideline for clinical trials [12], and the International Committee of Medical Journal Editors launched a clinical trial registry [13]. Such kinds of progress in the circumstances of clinical trials have enabled for investigator-initiated clinical trials in general practice.

The Adequate Treatment of Osteoporosis (A-TOP) study group was established in 2000 [11] in affiliation with the Japan Osteoporosis Society and organized a team for clinical trial management. The team consisted of clinical investigators (planning and analysis), foundation (funding) managers, officers from non-profit organization (data management) and several companies (data collection). This was the first joint team to create the post-making evidence for osteoporosis. In November 2003, A-TOP initiated a randomized clinical trial referred to as the Japanese Osteoporosis Intervention Trial (JOINT). The purpose of JOINT was to confirm the clinical significance of concurrent use of osteoporotic drugs. The first protocol, named JOINT-01, was initiated in 2002, but was suspended the following year due to a change in drug labeling. A second protocol, named JOINT-02, was established to clarify the effect of adding 1-alpha-hydroxycholecalciferol (alfacalcidol) to alendronate (ALN), using the incident fracture rate as the primary endpoint. In this paper, the rationale, organization and study design of JOINT-02 are introduced.

Rationale and aims

In 2002, the Japan Society of Osteoporosis sent a letter to randomly selected practitioners and enclosed a questionnaire regarding whether concurrent treatment using bisphosphonate and another drug was being utilized to treat osteoporosis. Surprisingly, 87.8% (79/90 practitioner) of the doctors who responded did have experience using concurrent treatment [14]. The most frequent drugs used in concurrent treatment with amino-bisphosphonate were alfacalcidol (93.7%), followed by calcitonin (50.6%), as there were expectations for these drugs to exhibit more potent inhibition of fracture occurrence or more significant increase in BMD, even though there was no apparent evidence. In addition to the lack of evidence related to fracture prevention, the safety profile of concurrent treatment had not been evaluated. Thus, evaluations of the effectiveness and safety of concurrent treatment were urgently required. Etidronate [15] and ALN [8, 9] were used as the drugs to confirm anti-fracture effectiveness in comparison to alfacalcidol in Japanese osteoporotic patients. However, these clinical trials were carried out at specific institutions and were initiated by experts in accordance with tight regulations. As a result, there may have been differences in the selected treatment and in the backgrounds of the patients between treatments conducted at these institutions and those conducted in general practice. In addition, the adherence of the treatment is expected to be lower in general practice than in institutions with experts who are committed to developmental trials. Thus, pragmatic study is urgently needed to evaluate whether bisphosphonates are effective to the same extent at the level of general practitioners as compared to the prior study (Phase III study).

Feasibility studies

The Japan Osteoporosis Society started discussions to execute a national clinical trial for obtaining evidence regarding the effectiveness of concurrent treatment in 2000. An executive committee of A-TOP was organized in 2002 and planned on forming a consensus regarding judgment standards for pre-existing fractures and incident vertebral fractures [16]. Morphometric criteria for incident fractures combined with a semi-quantitative assessment were thought to provide useful information on the study of clinical osteoporosis, especially for international comparisons. Next, to assume the number of participants in the clinical trial, the incident fracture rate and the risk of incident fracture were analyzed in the patient population, and the number of participants with sufficient statistical power [17] was calculated. Bone resorption marker was an independent risk factor for incident vertebral fractures in Japanese women. When the newly discovered risk factor was incorporated into the inclusion criteria in addition to conventional selection criteria such as age, prevalent fractures and bone mineral density, a reduction of about 40% in the estimated sample size was achieved. Thus, measurement of bone resorption markers is useful in reducing the sample size and the observation period in fracture-prevention studies carried out for developing drugs used to treat osteoporosis.

Materials and methods

Study design

Objective

JOINT was the first national, prospective, randomized, multicenter, open-labeled, blinded endpoints, controlled trial for osteoporosis made up mainly of practitioners of investigators in Japan. The objective of JOINT-02 was to clarify additive efficacy in terms of fracture prevention and safety, QOL and adherence in simultaneous use of alfacalcidol and ALN.

Subjects, intervention and endpoints

Confirmations regarding the patients were made by practitioners based on the inclusion and exclusion criteria (Table 1) after obtaining written informed consent. The

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Postmenopausal osteoporosis[a]
Over 70 years old
Ambulatory patients who do not require any help
Able to answer QOL questionnaire
Corresponds to more than one of A-TOP's risk factors for fracture[b]
Exclusion criteria
Metabolic bone diseases other than osteoporosis[c]
Contraindication to the drugs (ALN or alfacalcidol)
Dysfunction in communication of intentions
Severe degenerative deformation of vertebra
Abnormal heart function
Abnormal hepatic function
Abnormal kidney function
Treatment of osteoporosis by bisphosphonate within 6 months prior to the present study

These thresholds were decided by risk analysis by the A-TOP research group

[a] Over 1 year after menopause

[b] Pre-existing vertebral fracture number ≥1; BMD ≤ Young Adult Mean -3 SD; Urinary DPD ≥7.6 nmol/mmol Cr; or NTX ≥ 54.3 nmol BCE/mmol Cr

[c] Hyperparathyroidism and hyperthyroidism were excluded

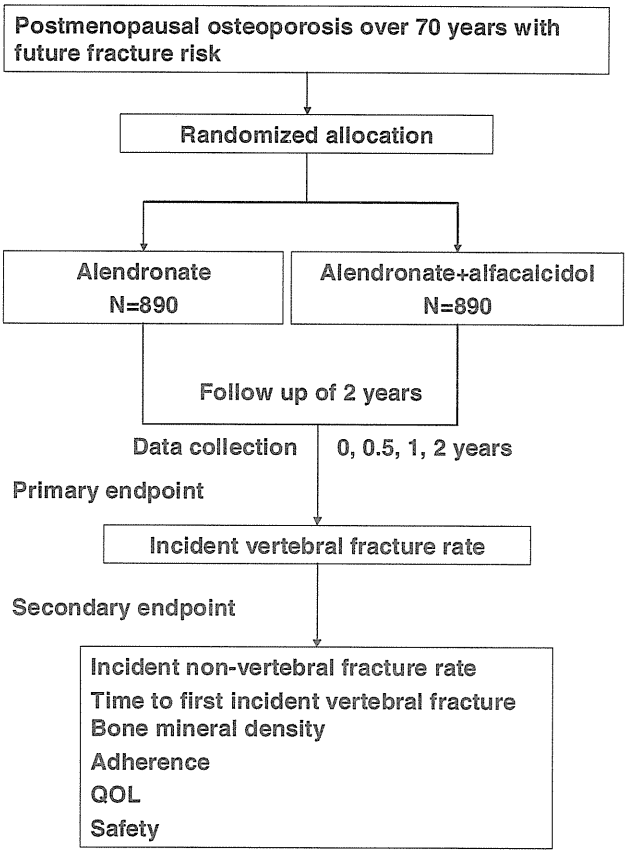


Fig. 1 Study design and outcomes

participants were selected by the practitioners and registered by Japan Clinical Research Support Unit (JCRSU), and then randomly allocated with a modified minimization method using age, number of pre-existing vertebral fracture number, bone mineral density (BMD) and value of bone metabolic marker into the group to be administered only ALN or the group that was to be administered both ALN and alfacalcidol. Registration and allocation of the participants were carried out on the Internet. After initiation of the assigned treatment, clinical data were collected at intervals of half a year for 2 years by I'cros Co., Ltd., through their visiting data collection service. Data were input to the database using a web system developed by ING Corporation. The primary endpoint was to compare the incident vertebral fracture rate between the intervention arms. The secondary endpoints were to compare the differences in the time to first incident vertebral fracture, non-vertebral fracture rate, bone mineral density, adherence, QOL and safety (Fig. 1). In addition, sub-group analyses categorized by baseline characteristics such as age, body mass index (BMI), serum 25-hydroxyl vitamin D levels, the number of pre-existing vertebral fractures and fracture grade were candidate factors. If participants wanted to change the designated treatment because of side effects or occurrence of fractures, they were permitted to do so, and follow-up observations were continued. Please see Table 1 and Fig. 1.

Sample size

Assumptions regarding the fracture rate in the ALN group were made based on a paper by Kushida et al. (Phase III trial for alendronate), in which it is reported that there was a 12.2% fracture rate during observations conducted over 2 years [8]. Since there are not much data on concurrent use of ALN and alfacalcidol [18], the authors' expectations were such that the effects of ALN would be added to those of alfacalcidol and that the hazard ratio of the alfacalcidol combined arm to ALN alone would be 0.64 [19]. The sample size was then estimated to be 890 cases per arm (two-sided alpha = 0.05, power = 0.8), taking account of a dropout rate of 10% referring to the value of the prior clinical trial of fracture intervention [4].

Fracture evaluation

X-ray films of conventional lateral radiographs of lumbar and thoracic vertebrae were taken and collected by I'cros Co., Ltd. After masking the patient's information, two