history, and body mass index [21]. Hip fractures are the most frequent type of fall-related injury, and risk factors for falls include age, muscle weakness, functional limitation, declined cognitive ability, environmental hazards, and a history of falls [22, 23]. There might be the possibility that persons with a high risk of osteoporotic fracture increased in 2004 compared to 1987/1988.

The incidence rate of hip fractures varies from region to region. The difference in incidence rates between countries or regions of countries can be ascribed to racial, cultural, and lifestyle factor [24]. The incidence rate in Okinawa was higher than those of other Japanese prefectures, such as Niigata [25] and Tottori [26], although it was lower than in Western countries [6, 14, 15]. Okinawa is known to have highest rate of obesity in young people in Japan, and increased morbidity of lifestyle-related disease [27, 28], such as heart disease, stroke, and diabetes, might increase the risk of hip fracture. Lifestyle changes within the geographical area could influence the hip fracture incidence rates.

It is important to investigate incidence rates at periodic intervals in order to identify trends over time and to assess osteoporosis prevention strategies. A major limitation of our study is that, as we only compared incidence rates between 1987/1988 and 2004, we were not able to analyze incidence rate trends over the whole time period in order to clarify recent changes. The hip fracture incidence rate has reached a plateau or even declined in some countries. For example, there has been a change in the trend in Scandinavian countries, where a further increase in the incidence rate was not found [14, 15]. In the US, the time trend is toward declining age-adjusted incidence rates [13].

It is important to consider the etiological difference between cervical and trochanteric fractures in developing appropriate approaches to the prevention of hip fractures, because trochanteric fractures are more closely related to osteoporosis and advancing age than cervical fractures [29–32]. Previous studies have compared the *C/T* ratios between countries and regions [7–11, 17–20, 25]. Many recent studies indicate that trochanteric fractures have increased more than cervical fractures [18, 25]. The present study also indicates that incidence rates of trochanteric fractures increase according to age, especially for women. The exponential increase in hip fracture incidence rates with aging could be related to decreasing bone mineral density and an increasing tendency to fall, especially in older patients with trochanteric fractures [6, 33].

Hip fracture should not be regarded as unavoidable event for a longer life. Thus, it is important to develop effective approaches for preventing or treating osteoporosis and for reducing the frequency of falling in order to decrease the incidence rate of hip fractures. José et al. [34] reported that, over a period of 14 years in Spain, the number of trochanteric fractures decreased and that of cervical fractures increased. They believed that the increase in osteoporosis drug use, the growth in the proportion of people older than 65 years engaging in physical activity, and the increase in average height caused a decrease in trochanteric fractures.

A major strength of this study was the availability of the data on hip fractures taken from the comprehensive hospital records of Okinawan patients. Our results include almost all incidents of hip fractures in Okinawa because all patients are admitted to local hospitals.

In conclusion, this study provided absolute numbers and age-adjusted incidence rates of hip fractures for Okinawa. These showed a dramatic increase compared with our previous data. It will be important to periodically investigate fracture incidence data to clarify trends in order to develop an effective strategy for the prevention of hip fractures.

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123 大腿骨近位部骨折の予防には認知症患者の転倒予防対策が必要である

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比嘉　丈矢[2]、坂元　秀行[2]、新垣　薫[2]、
金谷　文則[1]

【目的】沖縄県における大腿骨近位部骨折の発生状況を明らかにし、大腿骨近位部骨折の予防対策を検討する。【方法】平成21年9月～平成22年4月に沖縄県内の21施設において大腿骨近位部骨折の診断で入院加療を行った50歳以上の患者550例を対象に性別、平均年齢、骨折型、受傷場所、内科合併症の有無、脆弱性骨折の既往の有無、骨粗鬆症治療の有無、受傷時間帯の調査を行った。また受傷前のADLをBarthel indexで、入院時の認知症の有無を改訂版長谷川式認知症スケール（HDS-R）で評価し、Barthel indexとHDS-Rとの関係を検討した。【結果】男性114例、女性436例、平均年齢82.4歳、骨折型は頚部272例、転子部263例、受傷場所は屋内283例、屋外134例、施設・病院など116例であった。合併症は有468例、無69例、脆弱性骨折の既往は有198例、無320例、骨粗鬆症の治療は有81例、無435例であった。受傷時間帯は6時～11時が186例、12時～17時が135例、18時～23時が93例、0時～5時が62例であった。Barthel indexは100点が185人、65～99点が181人、21～64点(自宅での生活困難)が133人、0～20点（介護の負担大）が47人であった。HDS-Rは21点以上が156人、15～20点（認知症疑い）が71人、10～14点（軽～中等度）が62人、5～9点（中～高度）が77人、4点以下（高度認知症）が145人であった。Barthel indexとHDS-R間にはr=0.681の相関関係が認められた。【考察及び結論】34%に骨粗鬆症性骨折の既往を認めたが、骨粗鬆症の治療が行われていたのは全体の15%で、薬物治療のさらなる普及が必要と考えられた。認知症が疑われたのは全体の83%で、このうち41%は高度認知症であった。受傷前ADLに制限がある高齢者ほど認知症の程度が強く、治療後の歩行能力の獲得に問題が生じる可能性が高いと考えられた。大腿骨近位部骨折の発生率を低下させるには、認知症を有する高齢者の転倒予防対策が急務と思われた。

治療目標と治療方針の立て方

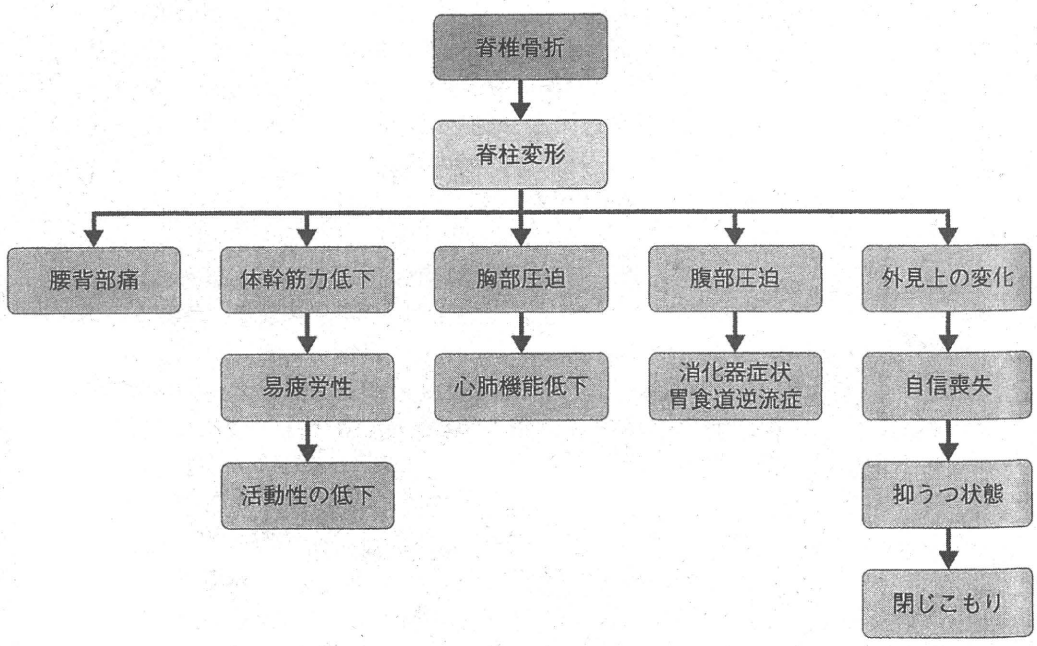
治療目標

骨折後の負の連鎖

- 骨粗鬆症では骨密度の低下や骨質の低下が生じ，骨強度が低下する．
- これに運動器自体の疾患や生理機能の低下による易転倒性が加わって，軽微な外傷で骨折をきたすようになる．
- 骨折すると身体機能が低下し，ADL や QOL が悪化する．
- 活動性の低下により身体機能がさらに低下し，自立した生活が徐々に失われる．
- 生命予後が悪化することも知られている．

椎体骨折

- 亀背や円背などの脊柱変形が生じ，❶に示す連鎖が生じる．



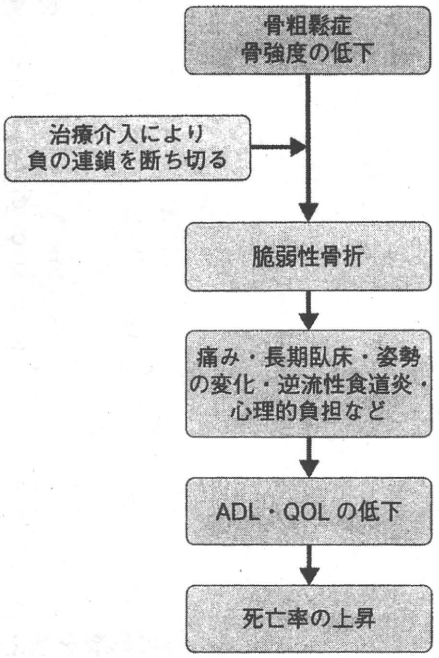
❶ 脊椎骨折後の負の連鎖
椎体骨折が複数個になると脊柱変形をきたすことが多く，さまざまな症状が出現する．その結果，QOL が低下する．

大腿骨近位部骨折

- 臥床による廃用症候群，認知症の発症や悪化，手術前後の合併症などが生じる．
- 患者の 10～30％は受傷後 1 年以内に死亡する．

治療目標は骨折の予防

- 骨折を予防することによって ADL や QOL の維持改善を図り，死亡率を低下させることが治療目標である（❷）．
- 骨折が複数回になるほど ADL や QOL への影響が大きくなるため，再骨折の予防はとくに意識すべき治療目標である．
- 骨密度が増加したからといって骨折が抑制されるとは限らず，骨密度の増加は治療目標ではない．



❷ 骨粗鬆症の治療目標は骨折予防である

治療方針の立て方

- 骨密度検査の結果だけを指標に治療方針を立ててはいけない．食事・運動指導はすべての患者に必要である．薬物治療は骨折リスクを評価し，基本的に高リスクの患者を対象に開始する．転倒リスクの高い患者には転倒予防を目的とした運動療法が必要である．

骨密度だけで骨折リスクを評価してはいけない

- 骨密度による骨粗鬆症の診断は，特異度は高いが感度は低い．
- 骨密度が正常でも脆弱性骨折をきたすことがある．
- YAM（young adult mean；若年成人平均値）の 70％未満よりも 70～80％のほうが骨折発生率は低いが，含まれる集団の人数が多いため 70～80％でも骨折する人は多い．
- 骨折患者数は，T 値が－2.5 以下（骨粗鬆症）よりも－2.5～－1.0（骨減少症）で多かったとの報告がある[1]．
- 骨密度だけでは骨折リスクの高い患者を見逃してしまう．

骨折リスクが高い人を対象に治療する

- 骨折リスクが高い患者における骨折予防が大切である．
- 骨折リスクが高い患者とは，骨折リスク因子を数多くもつ人である．
- 骨粗鬆症の患者を見つけるというよりも，骨折リスクの高い患者を見つけるつもりで診療する．

評価すべき骨折リスク因子（❸）

- 低骨密度を除く骨折リスク因子は，原則として骨密度を介さずに骨折リスク

❸ 骨折のリスク因子

1. 年齢
2. 性別
3. 低骨密度
4. 低 body mass index
5. 既存骨折（とくに大腿骨近位部，手関節，椎体骨折）
6. 両親の大腿骨近位部骨折
7. ステロイド使用（3 か月以上）
8. 現在の喫煙
9. 過度のアルコール摂取（1 日 2〜3 単位以上）
10. 続発性骨粗鬆症
    関節リウマチ，性腺機能低下症，炎症性腸疾患，長期臥床，臓器移植，I 型糖尿病，甲状腺疾患，慢性閉塞性肺疾患など
11. 骨代謝マーカー高値

に影響を与える因子である．

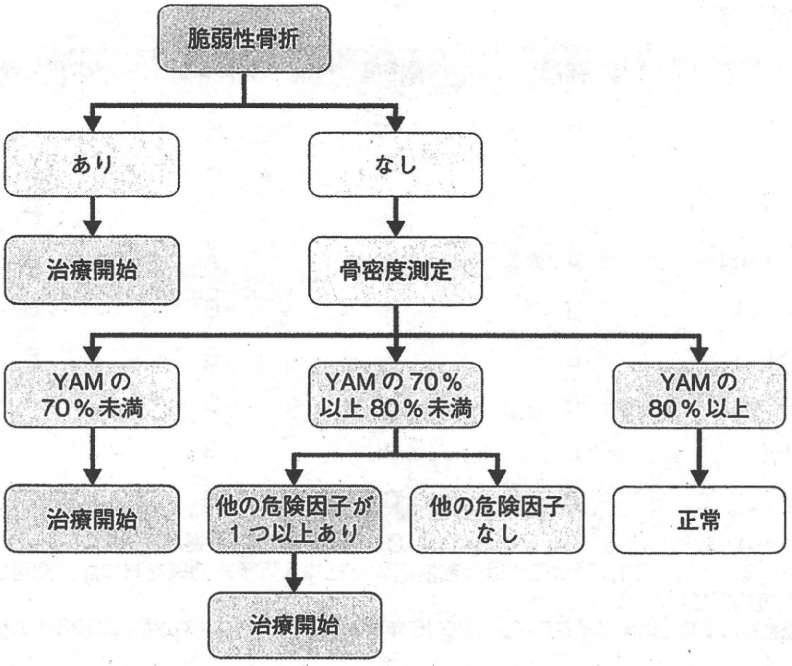
- 相対リスクの大きさから判断すると，年齢，既存骨折，低骨密度，ステロイド使用，両親の大腿骨近位部骨折の 5 つの因子が重要である．
- 骨密度が同じでも，高齢になるほど骨折リスクは増加する．
- 骨密度が YAM の 70 % のとき，FRAX® (fracture risk assessment tool) による 10 年以内の骨粗鬆症性骨折の発生率は 50 歳で 5 %，70 歳で 13 %，80 歳では 20 % になる．
- 椎体骨折，大腿骨近位部骨折ともに骨折リスクは女性が高い．
- 骨密度が 1 標準偏差低いと，骨折リスクは 1.5〜2.5 倍になる．
- BMI（body mass index）20 以下のやせた高齢者は，BMI 25 以上の高齢者と比べて，大腿骨近位部骨折のリスクは 1.4 倍になる．
- 部位にかかわらず既存骨折があると骨折リスクは 2 倍，既存骨折として椎体骨折があると椎体再骨折のリスクは 4 倍になる．
- 喫煙する高齢者は骨折リスクが 1.3〜1.8 倍になる．
- 1 日 2 単位以上のアルコールを摂取する高齢者は，骨折リスクが 1.2〜1.7 倍になる．
- ステロイドの服用歴がある高齢者は，骨折リスクが 1.7〜4.4 倍になる．

▶FRAX® については，p.200 参照．

Column 椎体骨折を見逃さない

骨粗鬆症性骨折のうち最も頻度が高いのは椎体骨折である．椎体骨折は無症状のことがあり，これを形態骨折とよんでいる．形態骨折は患者本人が自覚していないことが多く，問診だけでは見逃してしまう可能性がある．既存骨折がある場合には再骨折をきたしやすく，治療方針も変わることから，できるだけ胸・腰椎の X 線撮影を行い椎体骨折の有無を確認したい．若いときと比較して 4 cm 以上の身長低下や亀背などがあるときには，X 線撮影は必須である．

▶p.49, p.68 参照．



❹ 薬物治療の開始基準
他の危険因子として，過度のアルコール摂取（1日2単位以上），現在の喫煙，大腿骨近位部骨折の家族歴がある．

- ステロイドの服用量が1日7.5 mg以上の場合には，椎体骨折と大腿骨近位部骨折の骨折リスクはそれぞれ5倍，2倍になる．
- 両親のいずれかに大腿骨近位部骨折の既往のある高齢者は，骨折リスクが2.3倍になる．
- 骨吸収マーカーが高い高齢者は，骨折リスクが1.9～2.2倍になる．

❺ 転倒のリスク因子

1. 年齢
2. 性別
3. 転倒の既往
4. 歩行能力低下
5. バランス機能低下
6. 視力低下
7. 聴力障害
8. 睡眠障害（夜間頻尿を含む）
9. 認知機能低下
10. 服用薬剤の有無
11. ビタミンD不足（血中25(OH)D低下）
12. 環境因子（障害物など）

骨折リスクを考慮した薬物治療の開始基準

- 骨折を生じる前に薬物介入する必要があるため，薬物治療の開始基準は骨粗鬆症の診断基準とは異なる．
- わが国の薬物治療の開始基準は，骨折リスクを考慮し❹のように定められている．
- 骨折リスク因子をどのように薬物治療の開始基準に活用するかは国ごとに異なるが，既存骨折があれば薬物介入するという方針はおおむね共通している★1．
- ❸の骨折リスク因子のうち，骨代謝マーカーを除く10の因子がFRAX®による骨折危険性の算出に組み込まれている（他項を参照）．
- 一般に低リスク患者に薬物介入するのはovertreatment，高リスク患者に薬物介入しないのはundertreatmentと考えられるが，個々の患者でさまざまな因子を考慮に入れながら治療方針を決めることが肝要である．

★1
アメリカやヨーロッパの骨粗鬆症診療ガイドラインは下記ウェブサイトで参照可能である．
- National Osteoporosis Foundation (http://www.nof.org)
- European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (http://www.esceo.org)

❻ 主な薬剤の推奨度

	総合評価	骨密度	椎体骨折	非椎体骨折
アレンドロネート	A	A	A	A
リセドロネート	A	A	A	A
ミノドロン酸水和物	—	—	—	—
ラロキシフェン塩酸塩	A	A	A	B
活性型ビタミン D_3 製剤	B	B	B	B
ビタミン K_2 製剤	B	B	B	B
エチドロネート	B	A	B	B
カルシトニン製剤	B	B	B	C
カルシウム製剤	C	C	C	C

推奨の強さは，A：強く勧められる，B：勧められる，C：勧めるだけの根拠が明確でない，D：勧められないに分類される．ミノドロン酸水和物は骨密度増強と椎体骨折予防効果をもつが，認可されてまもないため推奨度の評価はない．

（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：2006[2]より作成）

評価すべき転倒リスク因子（❺）

- 骨粗鬆症性骨折の多くは転倒によって生じるため，転倒のリスク評価も必要である．
- 大腿骨近位部骨折の約7割は立位からの転倒によって生じる．
- 転倒リスク因子は加齢に伴う生理機能の低下に関与するものが多く，定量化が困難である．
- 転倒の既往と睡眠障害，睡眠薬の服用は，転倒の予知にとくに重要である．
- 加齢によりバランス能力および移動歩行能力に低下が生じ，閉じこもり，転倒リスクが高まった状態を運動器不安定症という．
- 転倒リスクを簡便に定量化する方法として開眼片脚起立時間があり，運動器不安定症の診断基準に含まれている．
- 開眼片脚起立時間が15秒未満では転倒のリスクが増大する．

治療の具体的方針

- 治療の基本は，食事・運動指導と薬物治療である．
- 骨粗鬆症の治療には，カルシウムとビタミンDが充足されていることが前提である．
- 高齢者では1日800 mg以上のカルシウム摂取が推奨されている[2]．
- 閉経後女性のほぼ1/3がビタミンD不足の状態にある[3]．
- ビタミンDの補充は虚弱高齢者の転倒予防に有効である．
- 骨折・転倒リスク因子の改善に努める．
- 薬物治療により骨強度を改善し，適切な運動療法を併用して活動性の維持・改善を図る．

Column リスク因子の軽減

骨折や転倒のリスク因子には修正可能なものと，修正不可能なものがある．修正可能な骨折・転倒のリスク因子として喫煙，アルコール摂取，ステロイド使用，低体重，服用薬剤，ビタミンD不足，筋力・バランス機能の低下，環境因子がある．治療では修正可能なリスク因子をできるだけ是正することが大切である．

- 薬物の選択は，椎体骨折，非椎体骨折に対する効果を評価し，エビデンスのある薬剤を選択することが基本である．
- 疼痛を有する場合にはカルシトニン製剤が有効である．
- 既存骨折を有する例ではエビデンスのあるビスホスホネート製剤あるいはラロキシフェン塩酸塩を使用する（❻）．
- 80歳以上におけるビスホスホネート製剤の骨折予防効果は実証されていない．
- 運動器不安定症を有する患者では，運動療法やヒッププロテクターなどの転倒予防対策が必要である．

（大湾一郎）

▶薬剤のエビデンスについては，p.153参照．

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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)

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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

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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

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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 $\leq$ Young Adult Mean -3 SD; Urinary DPD ≥ 7.6 nmol/mmol Cr; or NTX $\geq$ 54.3 nmol BCE/mmol Cr

[c] Hyperparathyroidism and hyperthyroidism were excluded

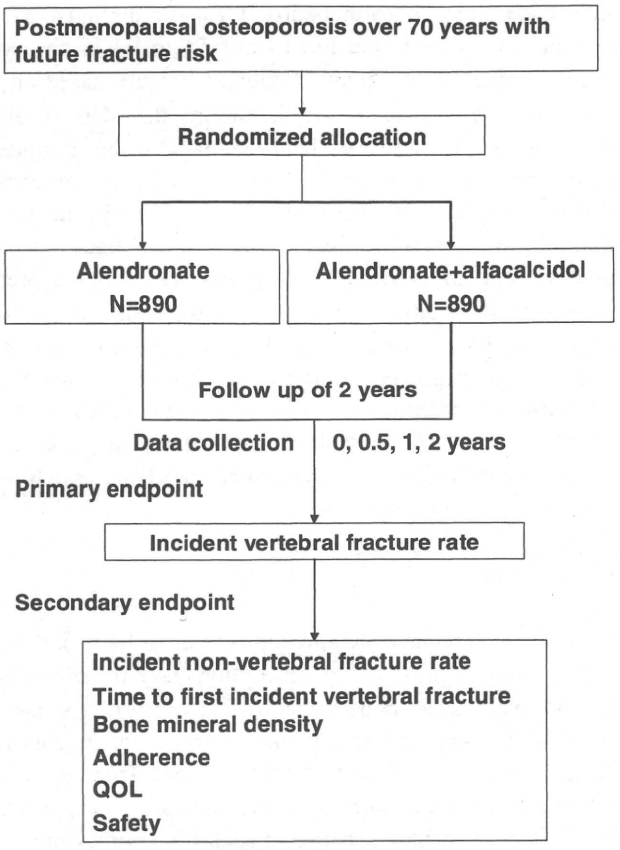

Fig. 1 Study design and outcomes

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

independent readers (orthopedist, TN and radiologist, MF) simultaneously reviewed films from T4 to L4 in chronological sequence and graded vertebral fracture based on a semi-quantitative method [20]. Before the start of the study, these two observers held meetings to make adjustments between their own criteria for grading vertebral fractures. When the diagnosis of pre-existing fractures made by the reviewers differed from those made by the practitioners, the reviewers' diagnosis was adopted preferentially. If inconsistencies arose between the readers in diagnosing pre-existing and incident vertebral fractures, the two readers negotiated between themselves to reach a consensus. Incident bone fractures other than those of the vertebrae were comprehended from the chart, and the occurrence of fractures was confirmed based on X-ray films or a record of the operation.

Clinical data

BMD at the lumbar vertebrae, hip (proximal femur), distal radius (dual energy X-ray absorptiometry) or left-sided second metacalpal bone (microdensitometry) was measured at baseline and at 6-month intervals for 2 years at each institute. The data of BMD obtained from the different machines and from different bone sites were calculated as the percentage change in each time point from the baseline value. The statistical difference in change of BMD between the group that received combined treatment and the group that was administered only ALN was compared based on each set of data for BMD for the different bone sites. Body height was measured at baseline, 12 and 24 months. Bone turnover markers (urinary type I collagen cross-linked N-telopeptide or urinary excretion of deoxypyridinoline) were measured at baseline and again 6 months after initiating treatment. QOL was assessed by using self-administered questionnaires (JOQOL and EQ-5D) at baseline and at 6, 12 and 24 months after initiating treatment [21]. Serum samples were sent to the central laboratory (SRL Co., Japan), and 25-hydroxyl vitamin D concentrations were measured. Other routine biochemical examinations were carried out at baseline and at 2 years after initiating treatment in order to estimate biochemical adverse events. All adverse events were reported to JCRSU, coded by MedDRA, and categorized as either "known" or "unknown." If an unknown adverse effect occurred, it was reported to the investigator and ethical committee.

Ethics and registration

Ethical issues regarding protocol were reviewed by the ethical committee for JOINT under the Declaration of Helsinki (Dr. Rikushi Morita, Chairman). If it turned out that a patient was at a disadvantage under observation, the ethical committee was given permission to stop the protocol. This study was registered at UMIN-CTR (University Hospital Medical Information Network—Clinical Trial Registry) with the number C000000001.

Statistical analysis

Analysis of the intent to treat principle was applied to the statistical analysis. Efficacy analysis uses a full analysis set (FAS), and all of the enrolled patients are applied to the analysis except for patients without efficacy data, patients who do not correspond to inclusion criteria and patients who do not receive treatment. The PPS (protocol per set) group is defined as consisting of patients without any serious protocol violation.

Recruitment of the practitioner

The explanatory meeting of the protocol and registration was held in all of Japan. The executive members of the A-TOP research group were responsible for the presentation of the protocol and for the recruitment of study institutions and practitioners. The A-TOP committee created the WEB site on the Internet so that the registration of the study could be executed directly. I'cros Co., Ltd., was also involved as a collaborator in calling practitioners.

Results and discussion

Several principles had to be considered for acceptance of concurrent treatment: firstly, the concurrent treatment should be clinically and statistically significantly more effective than the basic treatment; secondly, the concurrent treatment should be of the same level of safety as single treatment; thirdly, the concurrent treatment should be cost-effective. Although these principles should be evaluated before adopting concurrent treatment, the authors have applied concurrent treatment to osteoporosis widely, without any background evidence. Among these principles, the authors have decided to evaluate the first two issues, effectiveness and safety, in the present study. Since this type of evaluation is absolutely required by a clinician, a researcher-initiative study was considered as being the most suitable type of evaluation. This was the reason why the authors decided to use a researcher-initiative clinical trial in determining the effectiveness of concurrent treatment for osteoporosis. The JOINT-02 protocol was the first randomized, controlled trial conducted nationwide for osteoporosis in Japan initiated by researchers, and its scale was also the largest ever. It was therefore necessary for various organizations to collaborate together, and there

have been no previous reports on how to manage the PROBE trial in Japan. This is why we wanted to report the design of JOINT-02. In this paper, we have presented the organization of the A-TOP research group and execution of the JOINT 02 protocol. This is because we believe that this report should help a researcher who is willing to build a new nationwide investigation that is constructed by an organization of clinical research work.

Since the primary aim of JOINT-02 was to determine whether concurrent treatment using ALN and alfacalcidol is superior to treatment using ALN alone in terms of fracture prevention, true ("hard") endpoints such as vertebral fractures or long bone fractures were selected as the primary endpoint. The diagnosis of whether vertebral fractures were present or not on the X-ray films was made by two independent reviewers who did not have any information about the patient; when the judgment of fractures was split between the two reviewers, the reviewers negotiated with each other. Identifying vertebral fractures is more difficult than identifying long bone fractures due to some cases of new vertebral fractures not showing clinical symptoms and the shape of the vertebral body making it difficult at times to recognize whether there is a fracture. Therefore, to avoid misdiagnosis, diagnosis of pre-existing and incident vertebral fractures was made by two different observers. In cases where there was a discrepancy in the diagnosis of vertebral fractures between the reviewers and the practitioner, which occurred with regard to pre-existing fractures, the reviewers' judgment was given priority over that of the practitioner.

Surrogate ("soft") endpoints such as change in BMD or bone turnover markers were considered to be inadequate as primary endpoints in making conclusive statements regarding the efficacy of concurrent treatment. In this type of study, the soft endpoint (BMD or biomarkers) will connect dropout bias less effectively than the case-selected hard endpoint, because such markers are not able to be made blind to the clinicians. Furthermore, previous studies indicate that changes in BMD or bone markers do not predict future fractures [22–24].

In recent literature, it has been reported that poor adherence of bisphosphonates leads to a decline in the beneficial effects of this drug on bone [25–28]. It is expected that in contrast to prior developmental trials, this current study may have a higher dropout rate, since in a researcher-initiative study, the registered practitioner is not forced to maintain adherence very strictly. As a result, adherence in the present study may resemble the actual circumstances of adherence to bisphosphonate treatment by a general practitioner. It will be interesting to determine whether adherence in this study modifies fracture prevention by alendronate.

Although a careful plan for this study has been set up, the results will be applied to osteoporosis patients with the same background as the present study population, but not adapted to the entire osteoporosis population. Despite this limitation, we believe that the results will give us very important information regarding the concurrent treatment of osteoporosis.

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癌)や AFP(肝細胞癌)は診断に役立つ。CEA や CA19-9 などの腫瘍マーカーのみでは原発巣を確定できないが，原発性骨腫瘍や造血器悪性腫瘍，骨髄炎などと鑑別が問題の場合に癌の存在を示せる。

確定診断のポイント

画像で骨転移の可能性があれば，腫瘍マーカーなどで癌の存在を確認，場合により生検で組織診断。組織学的に骨転移癌と診断，原発不明の場合，腫瘍マーカーの検索と同時に，理学的診断(甲状腺癌，乳癌)と胸部と腹部 CT で腫瘍像の有無を確認。また，内視鏡で消化管癌の存在を検索。

鑑別すべき疾患と鑑別のポイント

1 原発性骨腫瘍(⇨ 1472 頁)
2 骨粗鬆症(⇨ 1476 頁)
3 感染性疾患：炎症症状(BSG，CRP 亢進)，脊椎では椎間板の狭小化，MRI による膿瘍の存在，穿刺による膿の培養。
4 骨 Paget 病：溶骨像から硬化像まで種々の画像を呈するが，多くは骨幅が拡大，骨梁の粗大化。ALP の上昇。組織所見は破骨細胞の増加と cement line の mosaic pattern。

なかなか診断のつかないとき試みること

組織診断のみでは，転移と原発性骨腫瘍，悪性リンパ腫，骨髄腫の鑑別に有用だが，原発巣までは発見できないことがある。有症状の骨転移には，治療と並行して原発巣検索も考慮すべきである。

予後判定の基準

最も信頼できる予後因子は原発腫瘍(肺癌，肝細胞癌，消化管の癌は予後不良，前立腺癌，乳癌，甲状腺癌は予後良好)。他の重要臓器(肺，脳，肝)転移の有無，転移数，全身状態(performance status)，病的骨折の有無などが予後因子。

合併症・続発症の診断

1 病的骨折：外傷性骨折と鑑別が重要。軽微な外傷でも発症，骨折部位に骨吸収像の存在。
2 脊髄麻痺：脊椎転移では，脊柱構築の破綻による不安定性と腫瘍浸潤による脊髄，神経根の圧迫で麻痺症状が発生。MRI により圧迫部位，腫瘍の範囲を確認。
3 高 Ca 血症：骨転移例の約 10～15%に高 Ca 血症を併発することがある。血清 Ca 値チェック。

経過観察のための検査・処置

骨転移しやすい腫瘍で無症状の場合，6 か月に 1 回，骨シンチグラム撮像。異常集積を認めれば，X 線と MRI で確認。不明確なら骨生検を行うか，時間をおいて再度画像評価。

治療法ワンポイント・メモ

1 治療目的は除痛と機能回復による QOL 改善。薬物療法，装具療法，放射線療法，手術療法がある。どれを優先するかは予後と骨転移状況で判断。
2 薬物療法にホルモン療法，化学療法，強オピオイド鎮痛薬(疼痛緩和)，ビスホスホネート製剤(骨転移の疼痛軽減，進行抑制，骨再形成)。
3 放射線療法は骨折準備状態に達していない場合や除痛目的，脊椎不安定性や神経圧迫がない脊椎転移例，手術に併用する場合も。また，外照射で制御不良の多発性骨転移(骨シンチ陽性)に β 線放出放射性医薬品(ストロンチウム 89)を注射。
4 手術は存命期間中に QOL 温存が保存療法のみでは得られないと判断できる場合に検討。

手術適応のポイント

QOL，生命予後を考慮し適応を決定。長管骨の骨折例，切迫骨折例，脊椎不安定性に起因する疼痛・麻痺例は，全身状態が許されるかぎり手術療法が適応。手術術式には局所根治手術と支持性のみ目的の姑息的緩和手術。術式選択には的確な予後予測が重要。局所根治手術は，転移巣が限局し，長期予後が期待の場合に適応。

さらに知っておくと役立つこと

骨転移癌は必ずしも末期癌ではない。ほかの重要臓器転移と比べて明らかに予後良好で，比較的長期生存例も稀でない。また，転移巣の根治手術で，延命が期待できるものもある。

骨粗鬆症・骨軟化症
Osteoporosis, Osteomalacia

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I 骨粗鬆症

骨折リスクを増すような骨強度上の問題をすでに

もっている人に起こる骨格の疾患(2000年，NIH)で，原発性と続発性骨粗鬆症(ステロイド性など)に分けられる。日本では1,000万～1,100万人罹患と推定。

診断のポイント

1低骨量：X線写真で骨萎縮・骨粗鬆症化，あるいは骨量(骨密度)測定で低値。
2脆弱性骨折：軽微な外力による骨折で部位は脊椎，大腿骨頸部，上腕骨頸部，橈骨遠位端，骨盤(恥骨，坐骨，仙骨)など。
3危険因子：高齢，既存骨折，アルコール摂取(1日3単位以上)，現在の喫煙，大腿骨頸部骨折の家族歴。
4身長低下，脊柱変形(亀背，姿勢異常)：最大身長から4 cm以上の低下は椎体骨折を示唆。rib-pelvis test，wall-occiput test。

移送の判断基準

脊椎椎体骨折で脊柱管内の脊髄を圧迫し，神経症状を呈している場合。

症候の診かた

1低骨量だけでは無症状。
2脊椎椎体骨折：腰部・背部痛(臨床骨折。動作時，荷重時に疼痛増悪，安静では軽減)，棘突起部に圧痛・叩打痛，脊柱変形。脆弱が高度では明らかな疼痛などの臨床症状を呈さずに骨折している例もある(形態骨折)。
3大腿骨頸部骨折：疼痛，立位・歩行不能となる。不全骨折では立位可能例もある。

検査とその所見の読みかた

1骨折の確認：X線，MRI，骨シンチが有用
2X線：脊椎椎体で骨粗鬆症化，大腿骨頸部で骨萎縮を認める
3骨密度：腰椎(L2～3，L1～4)，大腿骨頸部あるいはほかの部位で測定し，YAM70%未満で骨粗鬆症。70～80%では疑い。
4血液検査：Ca，iPは基準値以内，ALPは基準値以内あるいは軽度高値(基準値の1.5倍以内)。ほかに異常を認めず。

確定診断/鑑別すべき疾患のポイント

他の疾患を除外，鑑別することで確定診断に至る。腰背部痛を呈する疾患(脊椎症など)，腫瘍(骨転移)，骨髄腫，骨軟化症，上皮小体(副甲状腺)機能亢進症などを鑑別。血液・尿検査，X線・MRIなどの画像検査が有用。

予後判定の基準

神経障害を有する例，多発性の骨折，脊柱変形(後彎)を有する例では予後不良。

合併症・続発症の診断

脊椎骨折：神経障害，呼吸機能障害，消化器障害(逆流性食道炎)，慢性腰痛。運動機能低下・廃用性萎縮，QOL低下。

経過観察のための検査・処置

画像検査，血液・尿(代謝マーカーなど)

治療法/手術適応のポイント

骨折予防とQOLの維持を目指す：栄養・運動療法を基本とし，必要に応じて薬物治療を行う。骨折に対しては通常の骨折治療に準じ，脆弱骨に配慮して保存的あるいは手術的治療を行う。神経障害に対しては除圧術などの対応を要する。

さらに知っておくと役立つこと

ステロイド性骨粗鬆症の日本におけるガイドラインは「経口ステロイド3か月以上使用または使用予定で，脆弱性骨折，骨密度80%YAM未満，プレドニゾロン換算5 mg/日以上，いずれか」の場合に治療を開始する。

II 骨軟化症

骨質の形成後(matrix formation)に，Ca，Pが沈着(石灰化；mineralization)するが，この石灰化が障害された状態がくる病(rickets；成長期で骨端線閉鎖以前)，骨軟化症(osteomalacia；成長完了以後で骨端線閉鎖完了後の成人)である。骨石灰化が障害され，骨脆弱性が亢進し，組織学的には類骨過剰状態を示す。

リン酸代謝はPHEX，FGF23により調節されており，これらの異常による病態がある(図1)。

分類：ビタミンD作用不全と低リン血性，その他(アシドーシスなど)に分けられる。

診断のポイント

1原因となりうる病態，疾患の有無を検索。ビタミンD欠乏，作用不全(食事内容，日光曝露不足，食物アレルギーなど)，リン欠乏，アシドーシス，消化

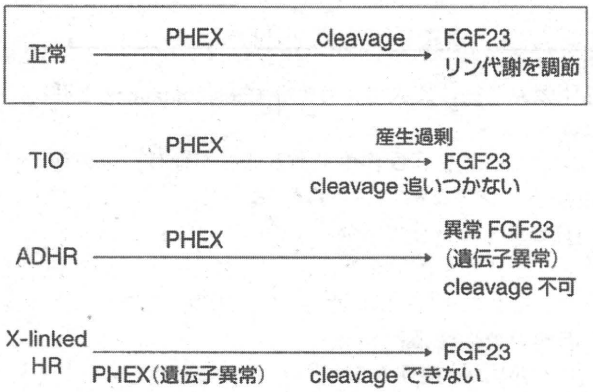

図1 低リン血症性骨軟化症における FGF23 と PHEX

管の吸収障害，肝・腎臓の機能障害，薬剤。
2 低身長，四肢変形(下肢 O 脚など)
3 血液検査で ALP(アルカリホスファターゼ)高値，画像検査(X 線)で特徴的な骨改変層(Looser zone)を認める。

症候の診かた

1 身体的には低身長，特に四肢(下肢)短縮，下肢変形(長管骨の彎曲，O 脚)，アヒル様歩行。
2 小児，乳児では胸郭変形，肋骨念珠，Harrison 溝，頭蓋軟化(craniotabes)。
3 成人では筋力低下などがみられる。
4 小児期に既往があり，成長完了以後，特に治療，通院などなく，突然に疼痛などで受診される例もある。

検査とその所見の読みかた/確定診断のポイント

1 既往歴の聴取(小児期)，生活歴(食事，日光曝露)，身体所見の診察。
2 血液・尿検査では，ALP(アルカリホスファターゼ)著明高値である。ALP 高値を示す「上皮小体機能亢進症，甲状腺機能亢進症，転移などの骨破壊性病変，Paget 病」などと鑑別する。くる病・骨軟化症では血清リンは低値。PTH，25(OH)，1,25$(OH)_2$D レベルは病態ごとに異なる。
3 単純 X 線では形態異常(長管骨の彎曲，骨陰影濃度の低下，骨端線の拡大・不整，骨幹端の透亮像を呈する。石灰化障害と負荷が加わると，骨改変層(Looser zone)が生じ，特に長管骨皮質部，大腿骨頸部，坐骨，恥骨などに認められる。
4 必要に応じて骨組織生検にて，確定診断に至る。

予後判定の基準

原因による。ビタミン D 不足では補充により改善する。低リン血症性ではリン漏出の程度が高度なとき骨変化も著明である。また腫瘍による例では，腫瘍摘出により改善するが，一方，腫瘍の発見が遅れたり，発見できない例では症状が続き，予後不良である。

経過観察のための検査・処置

画像検査(X 線)：石灰化障害，Looser zone の所見の変化，血液(ALP，iP)検査。

治療法/手術適応のポイント

小児(くる病：骨端線閉鎖完了以前)では骨成長障害，骨端線の著明な拡大の所見がある例に薬物療法，ビタミン D 製剤：1α-(OH)D_3，1,25$(OH)_2D_3$の単独あるいは中性リンの併用。高カルシウム血症に注意する。

原則として薬物は成長完了まで続けるが，成長完了以後，成人で骨痛，骨改変層，骨折を認めた例では，一定量のビタミン D の継続投与を行う。

O 脚などの下肢変形高度では膝関節，足関節への負担が過度にかかることから，矯正骨切術が適応となる。下肢の高度短縮では骨延長術が適応となるが，慎重に判断する。

さらに知っておくと役立つこと

成人では靱帯の骨化(後縦靱帯骨化症など)を合併する例もあり，神経所見に留意する。

薬物療法の継続期間については少なくとも症状，Looser zone などの所見がある場合には継続して薬物治療を行うことが望ましいと考える。

コンパートメント症候群(筋区画症候群)*

Compartment Syndrome

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急性型と慢性型がある。

治療方針

脊柱側弯症

発生頻度は50～60%。側弯症に加えて後弯を含む矢状面変形を伴いやすい。進行する側弯に対する装具治療は成績がよくない。進行例には手術治療を行うが，心疾患を伴うことが多いため，あらかじめ心肺機能の十分な評価が必要である。

外反扁平足

発生頻度はおよそ25%。扁平足自体で機能障害を生じることは少ないが，足長が長く，幅が狭いため既製靴が合わないことが多い。

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骨軟化症 OMIM番号：259660

Osteomalacia

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【疾患概念】 骨では骨質の形成（matrix formation）ののちに，ミネラル（カルシウム，リン）の沈着と石灰化（mineralization＋calcification）が起こる。この骨石灰化が障害されると，骨脆弱性の亢進と骨形成の障害がみられ，組織学的には類骨過剰状態を呈する。成長期で骨端線閉鎖以前ではくる病，成長完了以後で骨端線閉鎖完了後の成人では骨軟化症osteomalaciaと呼ばれる。

分類：ビタミンD作用不全と低リン血症，その他（アシドーシスなど）に分けられる。

① ビタミンD作用不全
- ビタミンD欠乏。
- ビタミンD　抵抗性くる病，Ⅰ型，Ⅱ型。

② 低リン血症（図7-33）
- 低リン血症性くる病。
  XLH　X染色体優性
  ADHR　常染色体優性
  ARHR　常染色体劣性
- Fanconi症候群
- 腫瘍性骨軟化症

③ 代謝性アシドーシス

④ その他：AI骨症など

【臨床症状と病態】

身体的には低身長，特に四肢（下肢）短縮，下肢変形（長管骨の弯曲，O脚），あひる様歩行がみられる。小児，乳児では胸郭変形，肋骨念珠，Harrison溝，頭蓋軟化（craniotabes）がみられる。一方，成人では筋力低下，筋肉痛，骨萎縮（脆弱性の亢進）などがみられる。

原因となりうる病態としてはビタミンD欠乏，作用不全（極度の偏食・ダイエット，日光曝露不足，食物アレルギーによる摂取不足など），リン欠乏，アシドーシス，消化管の吸収障害，肝・腎臓の機能障害，薬剤などがある。

問診で聞くべきこと

小児期に既往があり，成長完了以後，特に治療，通院などなく，突然に疼痛などで受診される例もあるこ

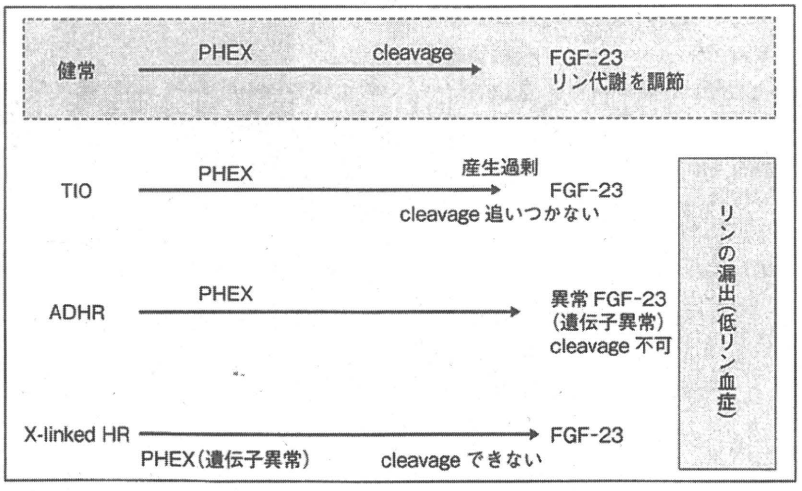

図7-33　リン代謝におけるFGF-23とPHEX