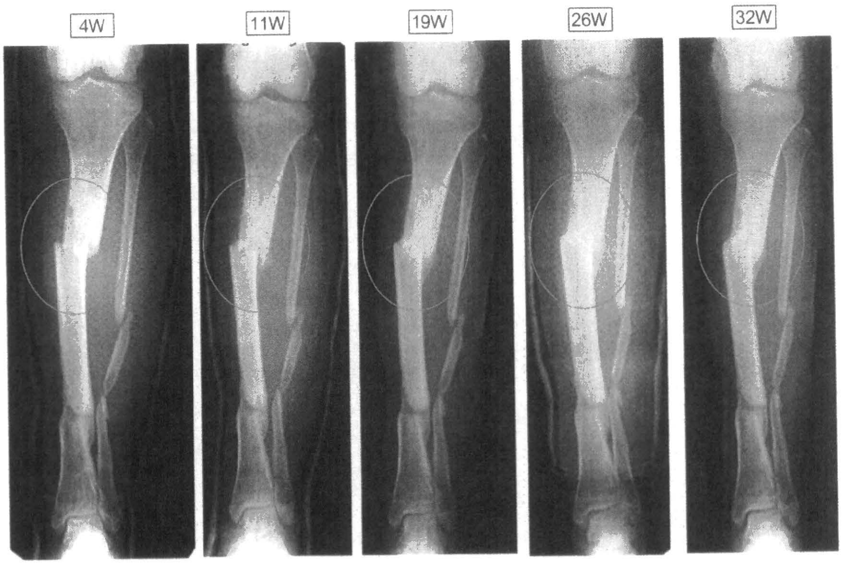

図 4-1　症例 1 の骨折部 X 線像の経時変化

24 歳女性。左脛骨近位部の骨折に対しギプスによる保存治療を行った症例の測定結果

（文献6より引用改変）

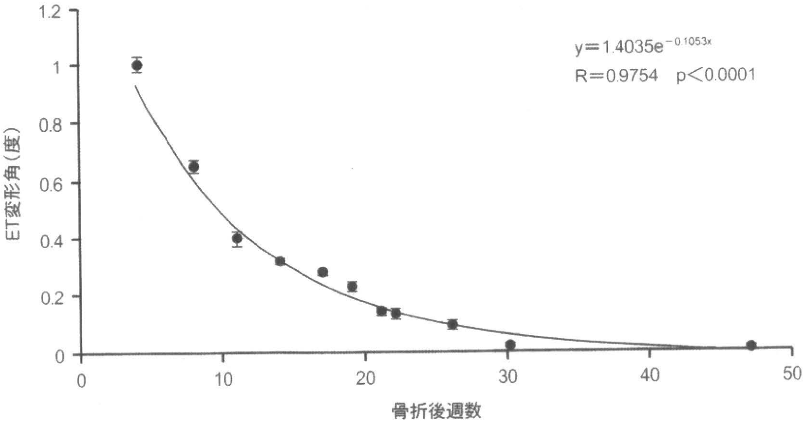

図 4-2　ET 変形角の経時変化

４週目より 11 週目まで急激なET変形角の減少を示し，その後も減少傾向が続き，21 週以降の測定では健常側より少ない ET 変形角を示した。

（文献6より引用改変）

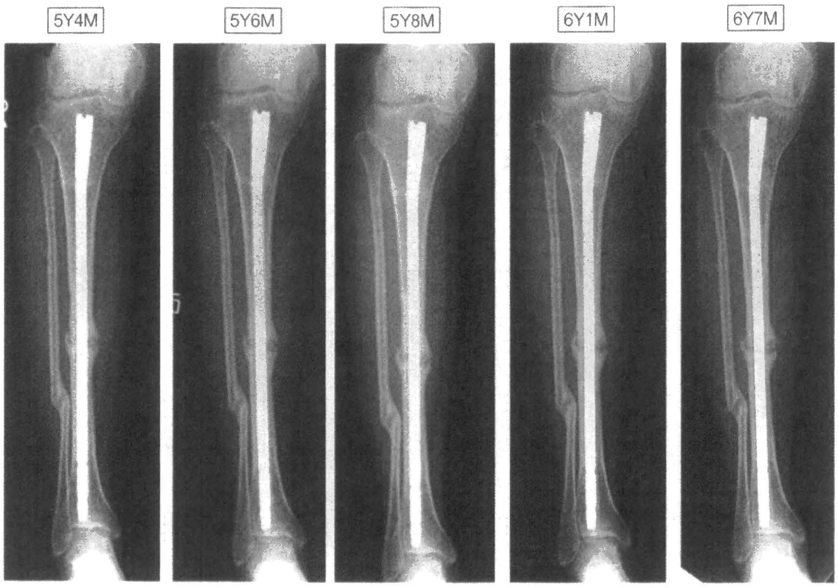

図 5-1 症例２のＸ線像の経時変化

26 歳女性。右脛骨骨幹部骨折に対して，髄内釘による内固定術が行われた。

（文献６より引用改変）

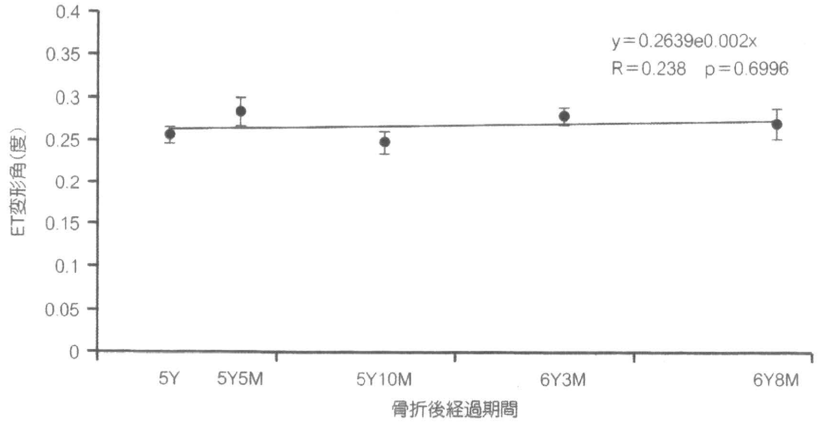

図 5-2　ET 変形角の経時変化

６カ月の経過にて明らかな減少傾向はなく，健常側に対しても常に５倍以上の変形角を示していた。

（文献６より引用改変）

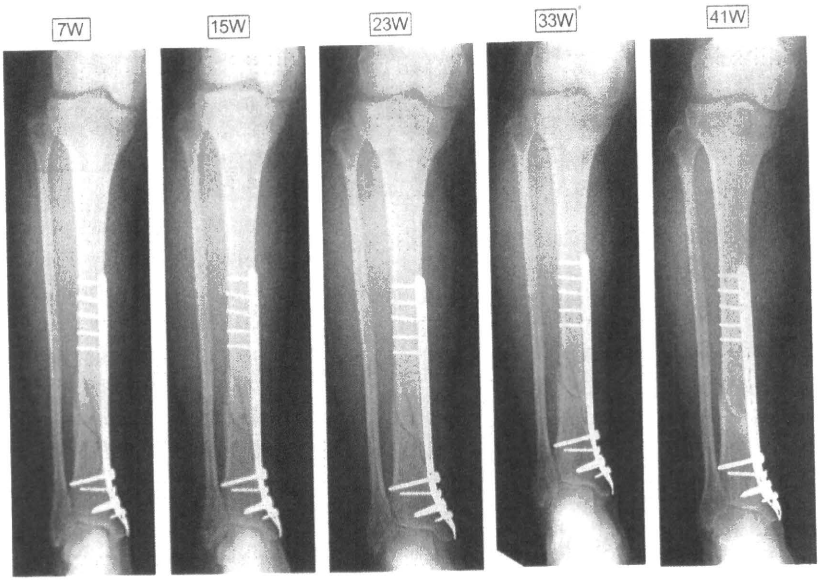

図 6-1　症例3の骨折部X線像の経時変化

右脛遠位部の骨折に対し，ステンレス製プレートにより固定を行った手術症例。

（文献6より引用改変）

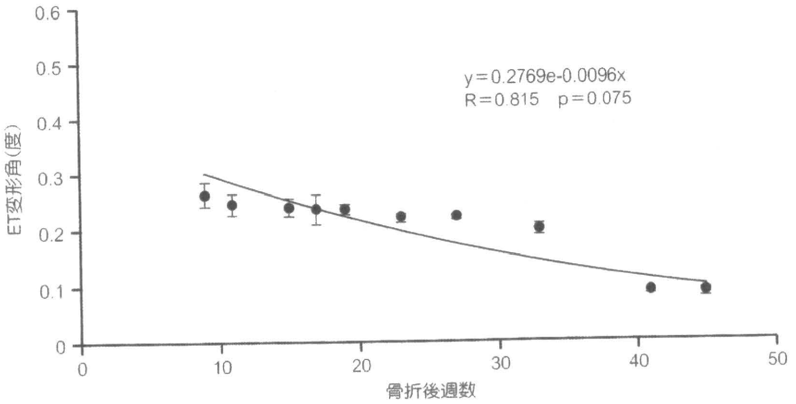

図 6-2　ET 変形角の経時変化

術後9週から 17 週の間に4回の計測を行った。8週の経過では ET 変形角の減少傾向はわずかであった。

（文献6より引用改変）

この3点曲げによるET計測により，骨癒合の進行と遷延を非侵襲に定量的に判別可能であった。既存の骨癒合判定法において非侵襲に骨の力学的特性を高精度に定量評価できたものはなく，このET測定により初めて測定が可能となった。

骨癒合判定を目的とし骨折患者を対象に測定を行っているが，ET計測の対象としては健常骨の測定も可能である。年齢により骨強度が低下することは周知の事実であり高齢化が進む現在，骨粗鬆症患者の数は急速に増加し，社会問題になっている。現在，骨強度を非侵襲に評価可能な測定法は存在せず，現状においてそのほとんどが骨密度(bone mineral density：**BMD**)測定により代用されている。しかし，BMD測定が強度と必ずしも相関しないことはすでに明らかにされている5)。ET計測による骨強度判定が可能となれば，その応用範囲は飛躍的なものになると考える。

おわりに

本法は，非侵襲に骨癒合の強度(剛性)を定量的に評価でき，骨癒合の経過を力学的指標で診断ができる。骨癒合の遷延や不全を診断できるとともに，今後の治療法の効果判定にも適応できると思われる。特定の骨折に対して，実施している治療が効果的かあるいは治療法を追加・変更する必要があるかどうかを，感受性高く評価できれば，常に最適な骨折の治療法を選択できる。そのための定量的診断法として有用性を発揮する可能性がある。

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特集：骨粗鬆症の薬物療法

定量的CTを用いた有限要素法による骨強度評価と薬剤効果判定

大西五三男

薬物療法総論　薬物治療の薬効評価と意義

定量的CTを用いた有限要素法による骨強度評価と薬剤効果判定

大西五三男

Prediction of vertebral strength using a CT based finite element method-clinical application in evaluation of the efficacy of alendronate

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Abstract

QCT-based nonlinear finite element method (CT/FEM) can accurately predict vertebral compressive strength *ex vivo*. Alendronate effects were also prospectively assessed using CT/FEM in 33 patients with postmenopausal osteoporosis who were treated with alendronate at a dose of 5 mg/day for 1 year. At 3 months, vertebral strength significantly increased by 10.2 % from baseline ($p<0.0001$). The minimum principal strain distribution showed that the area of high fracture risk decreased. At 1 year, the density of the inner cancellous bone increased by 8.8 % ($p=0.0013$), while the density of the juxta-cortical area increased by 13.6 % ($p=0.0004$). CT/FEM detected alendronate effects at 3 months. Alendronate altered density distributions, thereby decreasing the area with a high fracture risk, resulting in increased vertebral strength.

Key words: CT based finite element method, osteoporosis, vertebral strength, alendronate, fracture risk

はじめに

骨粗鬆症に対する薬剤の効果を評価する場合，骨折発生率の抑制にどの程度有効であったかを評価できることが最も重要な評価指標であることは言うまでもない．しかし，これは多数の症例を対象にした2-3年という長期にわたるメタアナリシスの結果を待って初めて明らかになる[1]．しかし，臨床の現場では，個々の患者に対して，特定の薬剤が有効であるか，更には骨折をどの程度予防しているかを，早期に感度・特異度高く診断できる方法が望まれる．

骨の強度は，現在，骨密度と骨質の両者で決定すると考えられている[2]．ここで，骨質とは骨密度に関係のない骨強度に影響する諸因子と定義されている．しかし，骨はナノ単位からミリ単位に至る階層構造をもつ臓器であり，それぞれのスケールにおいて種々の骨強度関連因子すなわち骨質関連因子が存在する[3-5]．例えば，ナノレベル以下の階層では，コラーゲン構造，コラーゲンのクロスリンキング，ミネラルのタイプや結晶構造，コラーゲンとミネラルの界面の性状などが骨質に関連し，ナノからミクロンのレベルでは，コラーゲンやミネラルの分布や配向，マイクロダメージのタイプ，量，分布などが関連し，ミクロンからミリのレベルでは，

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微細構造，多孔性，皮質骨の厚さ，骨小腔の数，サイズ，分布などが関連し，ミリ以上のレベルでは，骨のサイズ，形状，また骨密度の量や空間分布が関連する．これらの種々の因子の関与によって，骨の材料としてのヤング率や降伏応力，また臨界応力などの材料特性の分布が異なってくることになり，骨全体としての強度に影響を与える[6]．当然のことながら臨床診断において考慮できる骨質関連因子は限られている．骨強度の臨床診断においては，このような種々の骨強度関連因子をより多く包含して考慮できる方法が理想的である．

dual energy X-ray absorptiometry(DXA), quantitative computed tomography(QCT)などの骨密度測定は，bone mineral content(BMC)や areal bone mineral density(aBMD)また volumetric bone mineral density(vBMD)を測定することができ，これらはある程度，骨の力学特性や骨折リスクを反映している[7]．しかし，骨粗鬆症治療薬の効果を判定する randomized clinical trial(RCT)では，DXAを用いた骨密度測定では十分に薬剤の骨折予防効果を評価できないと指摘されている．すなわち，aBMDの増加は薬剤の骨折予防の効果をわずかしか評価できていないという[8-10]．例えば，alendronateの脊椎椎体骨折予防効果に関するCummingsらのメタアナリシスに関する総説では，閉経後骨粗鬆症の女性に対してalendronateの投与後1年に，脊椎椎体の骨密度はplaceboとの比較において3.9%増加した[6,11]．更に3年後の試験終了時にはalendronateは椎体骨折の危険度を47%減少した．結果として椎体骨密度の増加は，alendronate投与による椎体骨折の危険度の減少のうち16%を説明できたにすぎなかった．risedronateでは3年間の試験後のaBMDの増加は4.3-5.8%であり，このことから予測された相対リスクは0.8程度であったが，実際に観察された骨折発生の相対リスクは0.5であり，現実には薬剤効果は骨密度によって予測したものより効果的であった．

骨粗鬆症の薬剤効果の判定を行う診断法として骨密度測定による診断法では十分でない可能性があり，更に感度・特異度の高い診断法が望まれる．近年，定量的CTデータを用いた有限要素法(CT/FEM)による骨強度評価が開発され[12]，一部の方法では臨床応用が始まっている[13]．予備的な結果からは，本法の感度・特異度はDXAよりも高いことが示されている[14]．

本稿では，CT/FEMについて解説し，本法を骨粗鬆症患者に対する薬剤効果判定に用いた予備的な臨床研究の結果について概説する．

1. 定量的CTを用いた有限要素法による骨強度予測診断

有限要素法は複雑な形状や構造をもった物体の強度を定量的に予測評価する方法として開発されている[15]．近年において，患者から取得した定量的CTデータをもとにして有限要素解析モデルを作成し強度解析を行う方法が提唱された[16]．これは患者固有の骨強度解析モデルといえるものである．

CT/FEMの方法を概説する．CT画像から解析対象の骨の形状と構造を抽出する．3次元の患者固有の骨のモデルを作成する．この3次元モデルは，ボクセルから構成されているが，すべてのボクセル内には対応するCT値が存在する．各ボクセル内のCT値は，同時に撮像された骨量ファントムのCT値から検量線を用いて，3次元骨密度値に置き換えられる．ここで，3次元の骨モデルは患者固有の形状・構造・骨密度分布を有する骨モデルになる．このデータを有限要素解析のソフトウェアに入力すると，有限要素モデルが作成される．骨の解析モデルの各要素内には，骨密度値が配置されているが，先行研究の骨密度対材料特性(ヤング率，降伏応力，および臨界応力)を関係づけるデータを用いて，骨密度は各材料特性に置き換えられる．ここで骨モデルは患者固有の材料特性分布をもつ解析モデルとなる．この骨モデルに対して仮想的な荷重や拘束条件を設定して，条件ごとに破壊(骨折)荷重を予測する．また予測骨折部位を表示することができる．

臨床用のCTを用いるために臨床応用が可能であり，有限要素解析を追加すること以外は全

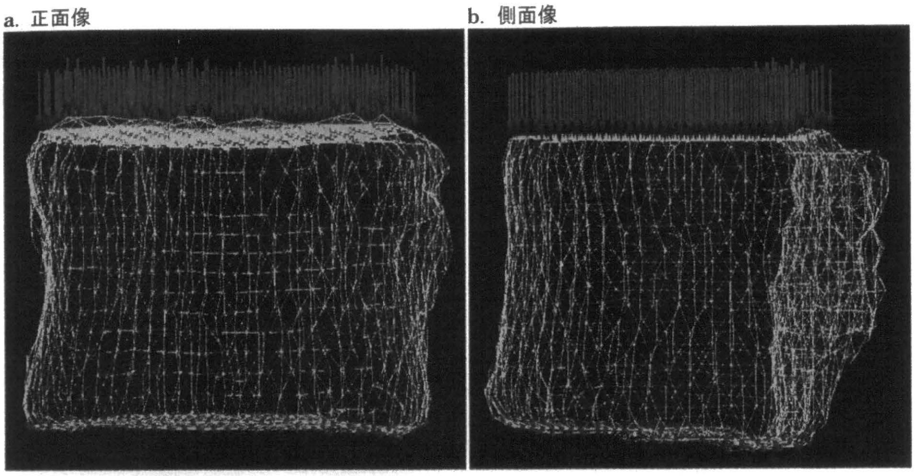

図1 単軸圧縮による荷重拘束条件

第2腰椎椎体の荷重・拘束条件を示す．椎体の頭側の終板から垂直に均一な分布の荷重を作用し，尾側の終板部分を完全に拘束する単軸圧縮条件を用いた．
(文献[18]より改変)

く定量的CTと同等の検査・診断法である．しかし理論的には臨床応用が可能であるが，現実には臨床で実用的な方法の開発までには至らず，方法の正確性の検証も十分ではなかった[17]．著者らは，臨床の現場で実用的でありかつ正確な結果を得ることができるCT/FEMを産学連携研究で開発し実用化した[18,19]．開発した方法の正確性について新鮮死体標本を用いて検証した[18,19]．結果として十分実用的な正確性を有することを実証した．この方法を予備的に臨床応用した．

2. 骨粗鬆症患者に対する薬剤効果判定への臨床応用—予備的な臨床試験—

原発性骨粗鬆症の患者に対して，ビスホスホネート製剤であるalendronateの効果をCT/FEMを用いて評価した．骨強度に影響する既往歴，薬剤歴がなく第2腰椎に骨折がない原発性骨粗鬆症の女性37人を対象とした[14]．alendronateを5mg/dayにて投与した．第2腰椎の椎体の予測骨折強度を評価対象とした．荷重条件は頭側の椎体終板に均一な垂直荷重が加わる単軸圧縮とした(**図1**)．CT/FEMによる予測強度の評価および同じデータを使うQCTによる第2腰椎椎体中央部のvBMDの評価を投与前・投与後3・6・12カ月時に，第2腰椎-第4腰椎正面のDXAによるaBMDの評価を投与前・投与後6・12カ月時に行った．更に，骨吸収に関して，骨代謝マーカーである尿中のN-telopeptide of type collagen(NTx)の測定を投与前と投与後3カ月において行った．12カ月を追跡期間として，その期間中に副作用などで投与継続できなかった2人および，第2腰椎に骨折が生じた2人を除外した33人(平均年齢76.5歳)について，alendronateの効果判定をCT/FEMとQCTおよびDXAの間で比較検討した．

骨粗鬆症患者33人に対するalendronate投与の結果，DXAによるaBMDの増加は投与後6カ月で平均3.7％(有意差なし)であり，12カ月では7.5％であり有意に増加した(paired t-test, $p<0.0001$)．またQCTによるvBMDの増加は，投与後6カ月で，5.1％(有意差なし)で，投与後12カ月で8.8％であり有意に増加した($p=0.0013$)．これに対して，CT/FEMによる椎体の予測強度は投与後3カ月で10.2％，6カ月で16.7％，12カ月で26.9％であり，それぞれ有意に増加した(Freedman test, $p<0.0001$)．CT/FEMによる予測強度は3，6，および12カ月のすべての時期で投与前よりも有意に増加した．

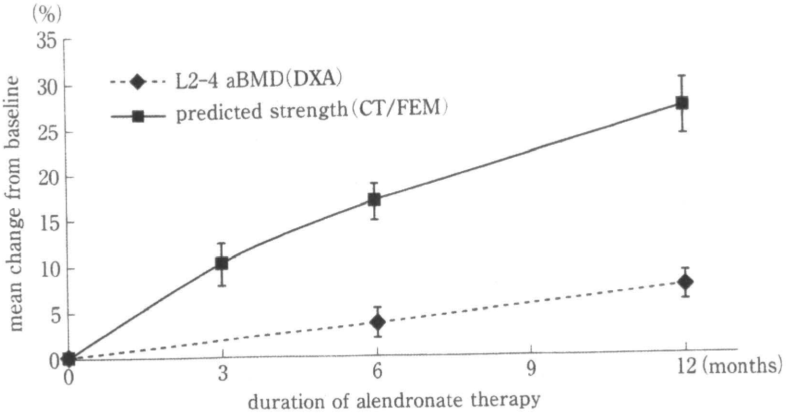

図2 CT/FEMによる予測強度とDXAによる骨密度の薬剤投与後の推移

alendronate投与後のCT/FEMによる予測強度と，DXAによる骨密度の推移を示す．予測強度は，投与3カ月時に投与前よりも有意に増加した．骨密度は12カ月時に有意に増加した．予測強度の増加率は，骨密度の増加率を大きく上回った．
（文献[14]より改変）

尿中のNTxは全例において投与3カ月で有意な減少があった($p<0.0001$)．このことから，CT/FEMはDXAやQCTよりも早期に感度高く薬剤効果の判定が可能であった(**図2**)．

Keavenyは，teriparatideとalendronateの治療効果をCT/FEMを用いて評価している．この臨床試験では原発性骨粗鬆症の女性25人に対して投与前，投与後の6カ月および18カ月でCT/FEMによる第3腰椎椎体の圧縮における予測強度を評価している．FEMの方法においては著者らの方法と異なるが，結果としてはalendronateによる骨粗鬆症の治療を最も感度高く評価したのはCT/FEMであり，次いでQCTによるvBMDによる評価であり，DXAによるaBMDの評価は最も感度が低かった[20]．このことは著者らの方法における結果と同様で矛盾はなかった．

これらの結果から，alendronateは骨密度を増加させるが，それ以上に脊椎椎体強度を増加させることが示唆された．このことは，alendronateなどの骨吸収抑制薬が骨密度の増加以上に骨折の発生を抑制したという複数の臨床試験の結果を支持する事実である．予測強度の方が骨密度よりも薬剤による増加が大きかった要因につき検討する．要因の一つは，DXAがaBMDの測定すなわち面積密度を計測し，CT/FEMはQCTのvBMDの体積密度のデータを用いることにある．先行研究においても，vBMDはaBMDよりも，より骨強度に相関が高いことが示されている[21]．Blackらのalendronateの効果をvBMDとaBMDの両者で評価した研究においてもvBMDの方が感度高く効果を評価している[22]．CT/FEMでは更にvBMDの分布に関する情報を加味して構造解析を行う．すなわち構造強度として評価する．そこで薬剤が密度分布や骨の構造を強度が増加する方向で効果を発揮すれば，当然，骨強度は単なる骨密度の増加を凌駕し，更に大きく増加することになる．著者らが行った予備的臨床試験において，患者の椎体骨の骨密度分布を検討すると，椎体の皮質シェルの近傍または同部の隣接部分に骨密度の増加領域が著明に存在した．また圧縮による骨折の危険が高い領域である最小主歪みの絶対値の大きい部分を見てみると，治療経過とともに，危険領域が減少していることが明らかであった．すなわち構造強度として圧縮破壊のリスクの高い各部位が治療とともに減少したことが明らかである．薬剤効果として，皮質シェル近傍部分で骨密度が特異的に増加して，圧縮応力の集中が軽減した結果，最小主歪み分布が改善

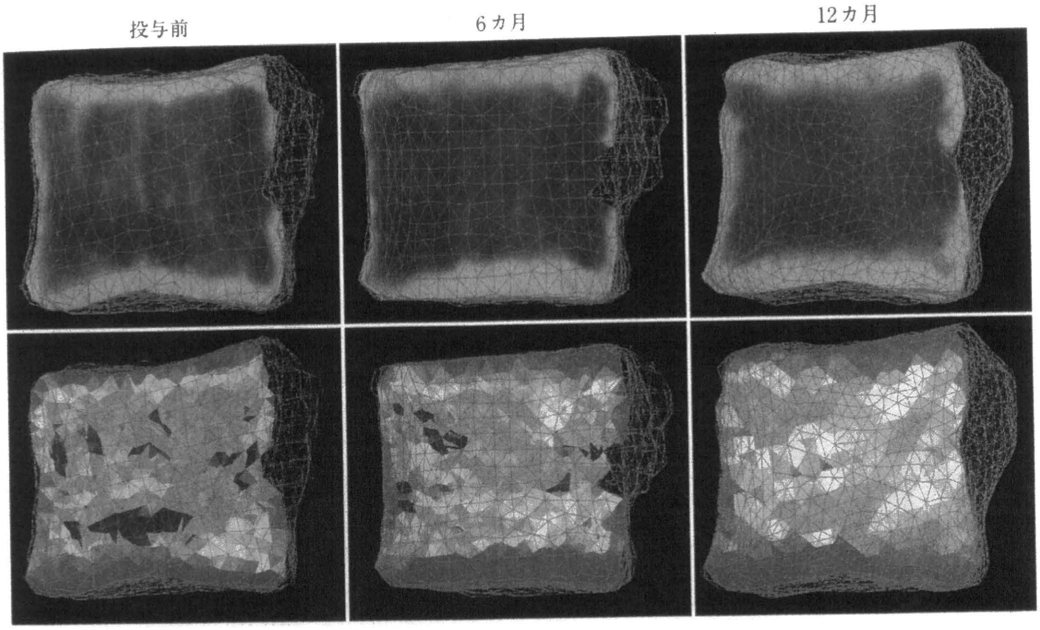

図3　Alendronate投与後の骨密度と最小主歪み分布

alendronate 5mg/day投与後の骨密度と最小主歪み分布を示す．症例は74歳女性で，第2腰椎側面を示す．骨密度分布の推移を上段に示す．1kNを圧縮負荷した状態の最小主歪みを下段に示す．カラースケールにおいて，青色の部分は最小主歪みの絶対値が大きく，骨折の危険が高い領域である．投与後，骨密度は椎体の周辺に増加し，骨折リスクの高い領域(青の部分)は経時的に減少した．
(文献14)より改変)

し，椎体強度が大きく増加したことが示唆される(**図3**)．DXAによるaBMDの評価ではとらえられない薬剤効果をCT/FEMでは評価できる可能性がある．

本稿で紹介したCT/FEMによる骨強度の評価法は，実質的な診断技術の内容としては，患者から検査対象の骨を仮想的に摘出して，それを仮想的な静的な荷重による力学試験にかけて強度を評価するというものである．これはある特定の患者が転倒したときに果たして骨折するのかどうかを判定するものではない．この判定を実現するためには，患者の転倒しやすい方向を確定すること，あるいは患者の皮下脂肪などの軟部組織の衝撃吸収能がどの程度であるか，また転倒に際してどの程度の衝撃力が作用するか，などについて正確な評価がなされなければならない．これを正確に行うにはまだまだ骨強度解析法において未解決の問題がある．今後はこのような評価ができる方法の進歩が必要である．しかし，現状でも十分に骨強度を指標とした評価ができるので，本法の臨床応用は確実に進めていく意義があると考える．

おわりに

本稿で紹介したCT/FEMによる骨強度の評価は，当然自然経過で骨強度が加齢とともに減少していく経過を追跡することも可能である．ただし，本法は定量的CTを行う必要があり，CTの撮影を必要とすることから，多数の検診者を対象にすることは現状では困難である．また骨強度の有限要素法解析には解析法を熟知した専門家の介在を要する．多くの検診者・患者に適用するには，まだまだ問題がある．しかし，CT装置の更なる普及や有限要素法解析が自動化されることで，より多くの検診者・患者に適用できるようになると考えられる．そうすれば近い将来において本法が大いに普及すると考えられる．

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● *Original Contribution*

A NEW METHOD FOR EVALUATION OF FRACTURE HEALING BY ECHO TRACKING

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Abstract—Assessment of bone healing on radiographs depends on the volume and radio-opacity of callus at the healing site, but is not necessarily objective, and there are differences of judgment among observers. To overcome this disadvantage, a clinical system was developed to quantify the stiffness of healing fractures of the tibia in patients by the echo tracking (ET) method in a manner similar to a three-point bending test. The purpose of this study was to ensure that the ET system could clinically assess the progress, delay or arrest of healing. The fibular head and the lateral malleolus were supported. A 7.5-MHz ultrasound probe was placed on the proximal and distal fragments and a load of 25 N was applied. Five tracking points were set along the long axis of the ultrasound probe at intervals of 10 mm. With a multiple ET system, two probes measured the displacement of five tracking points on each of the proximal and distal fragments of the tibia, thereby detecting the bending of the two fragments generated by the load. ET angle was defined as the sum of the inclinations of the proximal and distal fragments. Eight tibial fractures in seven patients treated by a cast or internal fixation were measured over time. In patients with radiographically normal healing, the bending angle decreased exponentially over time. However, in patients with nonunion, the angle remained the same over time. It was demonstrated that the ET method could be clinically applicable to evaluate fracture healing as a versatile, quantitative and noninvasive technique. (E-mail: ohnishii-dis@h.u-tokyo.ac.jp) © 2008 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasound, Echo tracking, Fracture site stiffness, Fracture healing.**

INTRODUCTION

The most important issue in assessment of fracture healing is to obtain information about restoration of the mechanical integrity of the bone. In clinical practice, fracture healing is usually judged from serial radiographs. Assessment of bone healing on radiographs depends on the volume and radio-opacity of callus at the healing site, but is not necessarily objective, and there are differences of judgment among observers. In addition, radiographs cannot evaluate fracture site strength. In these respects, assessment of fracture healing by using radiographs is far from ideal.

The stated disadvantages of radiography for assessment of fracture healing have been pointed out in recent years, and various other methods of assessment have been developed. Jernberger (1970) devised an invasive method for measuring the bending stiffness of healing fractures of the tibia. With his method, the proximal and distal bone fragments were fixed by screws that were connected to a specially designed beam, and a load was applied through a screw at the center of the fixing screws. The method was based on the principle governing the bending of two beams connected at the ends and subjected to a bending force applied at the midpoint. Burny et al. (1984) developed a method that used a strain gauge attached to a fixator shaft. With their method, the strain gauge readings were monitored over time during weight bearing, and the pattern of fracture healing was classified into seven categories (such as normal, delayed, arrested, *etc.*). Assessment using acoustic emission (AE) was developed by Nicholls and Berg (1981), who detected acoustic pulses generated by microscopic failure of the bone under loading. The investigation by Watanabe et al. (2001) revealed that AE signals occurred with the yielding of callus. However, the strain gauge method and the AE method have the disadvantage that both are limited to patients with external fixation, and both require the in-

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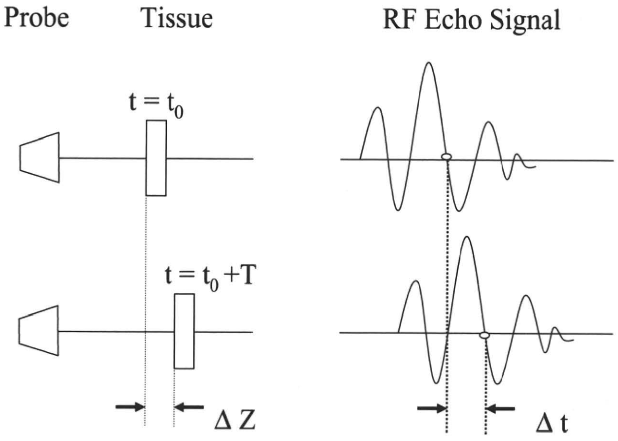

Fig. 1. The target tissue may move closer to or away from an ultrasonic probe over the distance ΔZ during a pulse repetition time of ultrasonic waves (T), causing phase delay of the RF echo signal (Δt). The ET method measures the extent of this displacement by tracking the initialized phase pattern of the echo signal.

sertion of screw pins or wires. For these reasons, such methods have not been widely used and a new method is needed that is both noninvasive and widely applicable.

To overcome such limitations, we developed a new method for the noninvasive and quantitative assessment of fracture healing. Bone always undergoes deformation in response to an applied load. By quantitatively measuring this deformation, it is possible to assess the mechanical properties of bone and thereby estimate the strength of a fracture site. In this study, we attempted to noninvasively assess the bending stiffness of the healing fracture sites after applying a load. To measure bending stiffness, we focused on ultrasound because it is noninvasive. Precise measurement of the displacement of a specific point can be done by the echo tracking (ET) method. This method is a technique for measuring minute displacement of a certain point on a tissue by detecting a wave pattern in the radiofrequency (RF) echo signal reflected from the target tissue (Fig. 1) (Hokanson et al. 1972). To apply this technique for detection of bone deformation, we improved it so that displacement could be measured with an accuracy of 2.6 μm (Matsuyama et al. 2006). We also developed a multi-ET system that was able to simultaneously track dynamic movement at multiple points on the bone surface. In our previous study of the three-point bending test using a porcine tibia, the strain gauge readings and the data from the multi-ET system showed an almost perfect linear correlation with the load ($r = 0.998$). These results indicated the possibility of using the echo tracking method to detect bone surface deformation.

The purpose of this study was to determine whether our newly developed ET system could clinically assess the progress, delay or arrest of healing by detecting the bending stiffness at the fracture healing site. Fracture healing was evaluated in patients with tibia fracture treated by a cast or internal fixation.

METHODS

A clinical system was developed to quantify the stiffness of healing fractures of the tibia in patients by the ET method in a similar manner to a three-point bending test. Five tracking points were set along the long axis of the ultrasound probe at intervals of 10 mm. With a multiple ET system, two probes measured the displacement of five tracking points on each of the proximal and distal fragments of the tibia, thereby detecting the bending of the two fragments generated by the load. ET angle was defined as the sum of the inclinations of the proximal and distal fragments (Fig. 2). When callus was weak in the initial stage of healing, the tracked points were almost in a straight line and the inclination of the two fragments was calculated directly. However, when the callus was more rigid in the late stage of healing, the line connecting the points was curved and the inclination was obtained from the slope of the linear regression equation for the displacement of the points.

Before clinical application of this method, its accuracy was evaluated by measuring the inclination of the metal flat panel.

Measurement of the accuracy of ET angle using an inclined flat metal panel

A flat stainless steel (SUS 420J) panel (length 270 mm, width 60 mm, thickness 5 mm) was used, which had a parallel accuracy and flatness variation of <2 μm. One end of the panel was attached to a magnet stand (DG, Noga Japan Ltd, Saitama, Japan), and the other side was attached to a goniometer (X13–001, Tsukumo Co. Ltd, Saitama, Japan) fixed to another magnet stand. Then, the

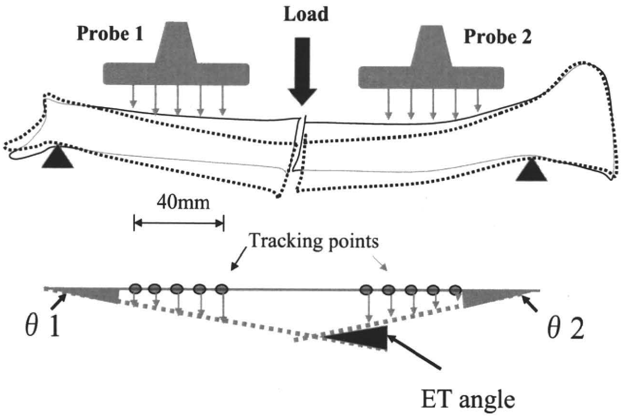

Fig. 2. Probes are set on each of the proximal and distal fragments of the tibia to detect the bending of the two fragments generated by a load. The ET angle is defined as the sum of the inclination of both fragments.

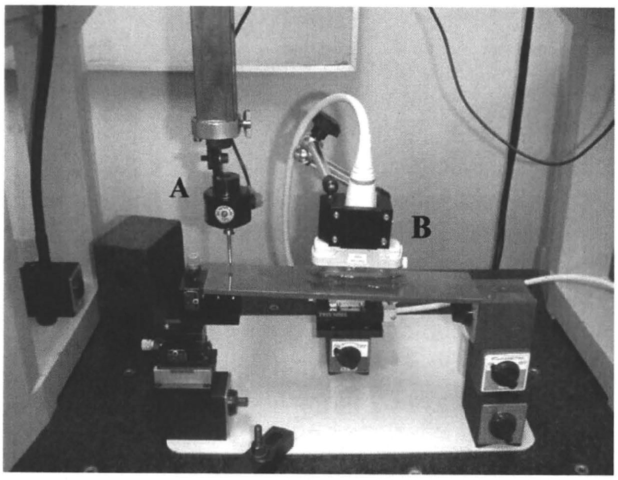

Fig. 3. The accuracy of the ET measurement was evaluated by measuring the inclination of the flat metal panel simultaneously using a 3-D measuring device. (A) 3-D measuring device; (B) 7.5-M Hz linear ultrasound probe.

metal panel was inclined by increasing the height of the goniometer stand. A 7.5-M Hz linear ultrasound probe (UST-5710-7.5, Aloka Co. Ltd., Tokyo) was set at a distance of 20 mm from the panel to measure the changes of displacement of each of five points on the panel (Fig. 3). Using these data, the ET angle of the panel was calculated. At the same time, the inclination of the panel was accurately measured using a 3-D measuring device (AE112, Mitsutoyo, Kanagawa, Japan) with an accuracy of 1 μm. The panel was inclined by elevating the sliding mechanism of the stand by 0.4 mm and the inclination of the panel was measured 5 times, after which the mean and standard deviation were calculated. Accuracy was evaluated by calculating the standard deviation of the difference between the ET angle and the inclination measured by the 3-D measuring device in each of the measurement trials.

Clinical measurement of fracture site bending stiffness

Eight tibial fractures in seven patients with an average age of 37 y (range 24–69 y) were measured (Table 1). Two fractures of two patients were treated conservatively with a cast, and six fractures of five patients were treated by internal fixation (locked intramedullary nailing in 4, plating in 1 and screws in 1). The average measurement period was 40.8 wk (21–60 wk), and the average number of measurements was 7.5 (5–11).

Patients assumed the supine position with both knees extended, and the affected leg was held horizontal with the antero-medial aspect of the tibia upwards. The fibular head and the lateral malleolus were supported and held tight by a Vacufix (Muranaka Medical Instrument Co., Ltd., Osaka, Japan) to avoid rotation of the leg during loading trials. Before measurement, B-mode images of the short axis of the proximal and distal fragments of the tibia were obtained to identify the center in both directions. By connecting both of the centers, the anatomical axis of the tibia was identified. A 7.5-MHz ultrasound probe was placed on the antero-medial aspect of each of the proximal and distal fragments in the long axis. Each probe was equipped with a multi-ET system with five tracking points at 10-mm intervals. The probes were set vertically on the skin of the leg and held tight with an articulated holder (DG61003, Noga Japan Ltd., Saitama, Japan). A load of 25 N was applied at a rate of 5 N/s and then reduced to 0 N at the same rate using a force gauge (DNP, Imada, Osaka, Japan) parallel to the direction of the probe at the most distal part of the proximal fragment adjacent to the fracture site (Fig. 4). For the initial measurement obtained in each patient, the loading point was set right on the long axis near the fracture site using a B-mode image as a guide. With this setup, the tibia was bent in the same way as for a three-point bending test in the direction of the ultrasound beam. In patients with oblique or spiral fractures, the loading point and the tracking points were set so that they did not cover the fracture site. In patients with a bone graft at the fracture site, the loading point was set on the graft, but the probes were placed so as not to cover it. In the patient with a plate, both the proximal and distal probes were set on the plate surface to measure bending of the plate. Using the multi-ET system, the probes

Table 1. Clinical cases of the tibial fracture

Case	Gender	Age	Limb	Treatment fracture healing	Measurement period (Initial-final)	Radiographic finding
1	F	24	L	Casting	4–47 wk	Normal
2	M	29	R	Casting	7–28 wk	Normal
3	M	23	R	Bone grafting	8–27 mo	Normal
4	M	31	R	Nailing	4–39 wk	Normal
5	F	57	R	Nailing	5–10 mo	Normal
6	F	57	L	Nailing	6–10 mo	Normal
7	F	26	R	Nailing	5 y 2 mo–5 y 7 mo	Nonunion
8	M	69	R	Plating	9–45 wk	Delayed

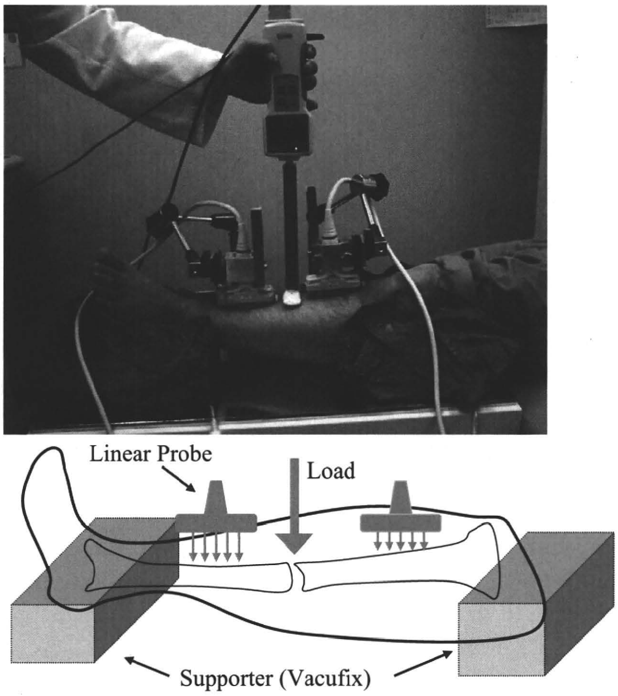

Fig. 4. The affected leg of a patient was held horizontal with the antero-medial aspect of the tibia upwards. The fibular head and the lateral malleolus were supported and held tight by a Vacufix. The probes were set vertically on the skin of the leg and held tight with an articulated arm. A load was applied using a force gauge parallel to the direction of the probe.

detected the angle between the proximal and distal fragments generated by the load. Measurement was repeated five times, and the mean and the standard deviation of the ET angle were calculated.

Fracture healing was assessed at intervals of two or three weeks until radiographic union or arrest of healing occurred. In each patient, the decrease of the ET angle was statistically examined to determine whether it decreased exponentially and whether the decrease was significant. To evaluate the changes of the ET angle over time, exponential regression analysis was performed, and the curve of the ET angle *vs.* time relation was drawn. Differences were considered significant when the p value was less than 0.05.

To investigate the influence of the position of the probes and the patient on the results, the precision of the method was evaluated by repeated measurement of the ET angle in a patient with a diaphyseal fracture of the tibia treated by a cast (case 2). In addition, the linearity of the relation between the load and the ET angle was assessed by incrementally increasing the load from 10 to 30 N. The ultrasound device (SSD 1000, Aloka Co. Ltd.) used in this investigation is used clinically and its safety has been established. The protocol of this investigation was approved by the ethics committee of The University of Tokyo Hospital, and the patients were enrolled after informed consent was obtained.

RESULTS

Accuracy of ET angle measurement for a flat metal panel

Measurement of the inclination of the flat metal panel showed that the average inclination was 0.117° and the standard deviation was 0.002°. The average inclination obtained with the 3-D measuring device was 0.116°, with a standard deviation of 0.003°. The standard deviation of the differences between the data obtained by the ET method and by the 3-D measuring device was 0.002°.

Clinical measurement of fracture site bending stiffness

The average time required for measurement was 17 min (range 15–20 min). At each loading trial, none of the patients complained of pain and there were no complications related to measurement.

The precision of this method was evaluated by repeating measurement of case 2 (treated with a cast), with repositioning of the leg and the ultrasound probes. The mean and standard deviation of the ET angle were 0.316 ± 0.015, and the coefficient of variation was calculated to be 4.6%. The linearity of the relation between the load and the bending angle was very high, with a correlation coefficient of 0.997.

Cases presentation

Case 1: A 24-year-old-woman treated with a cast. The patient sustained a spiral fracture of the proximal diaphysis of the tibia in a traffic accident, and a patella tendon bearing brace cast was applied. Healing was assessed by the ET method, as well as radiographs a total of 11 times from 4 weeks to 47 weeks after fracture. The fracture line became opaque and the callus volume increased from 4 weeks to 19 weeks, but after 26 weeks there was almost no change of the thickness of the callus. On the other hand, measurement showed that the ET angle was about 1° at 4 weeks, and that it decreased exponentially ($y = 1.40e^{-0.105x}$, $r = -0.975$, $p < 0.0001$). The ET angles of both cases 1 and 2 treated with a cast decreased exponentially over time and they reached the level of the intact side by 22 weeks (Fig. 5a, b).

Case 7: A 26-year-old-woman with a fracture of the diaphysis of the tibia treated by a locked intramedullary nailing. ET measurement was performed five times from 5 y 2 mo to 6 y 7 mo after fracture. Her X-ray films showed hypertrophic nonunion, but judgment whether healing was proceeding was extremely difficult. ET measurement showed that there was no significant decrease of the angle over a period of 1 y and 5 mo ($y = 0.264e^{0.002x}$, $r = 0.238$, $p = 0.700$) (Fig. 6a, b).

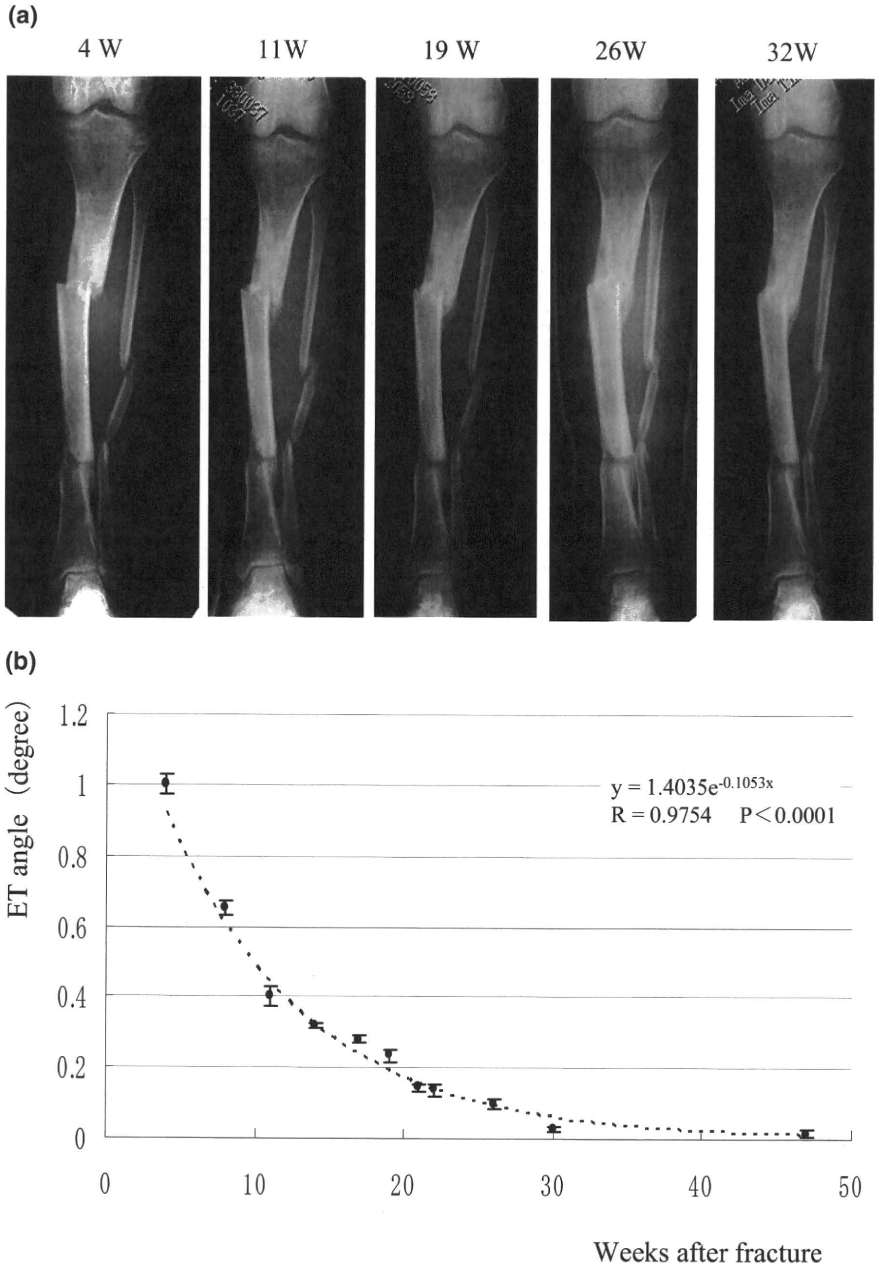

Fig. 5. (a) Time sequential change of the fracture site X-ray from 4 weeks to 32 weeks after fracture in case 1 treated with casting. The fracture site healed normally. (b) In the same patient, the ET angle was plotted. The ET angles decreased exponentially over time.

Case 8: A 69-year-old-man with a long oblique fracture treated with a plate. His X-ray films showed a long oblique fracture line extending for almost 80 mm. Measurement was performed 10 times from 9 weeks to 45 weeks after fracture, during which period almost no change of the fracture site or callus was recognized on X-ray films. The ET method measured the bending angle of the plate. The change was very slow, but the angle decreased significantly from 0.28 to 0.2 degrees, and then finally declined to 0.1 degree. The overall change showed an exponential curve ($y = 0.40e^{-0.030x}$, $r = -0.895$, $p = 0.0005$) (Fig. 7a, b). In patients with radiographically normal healing, the bending angle decreased exponentially over time (Fig. 8). However, in patients with nonunion, the angle remained the same over time.

DISCUSSION

Our method allows noninvasive assessment of bending stiffness at the healing site, so it can be appli-

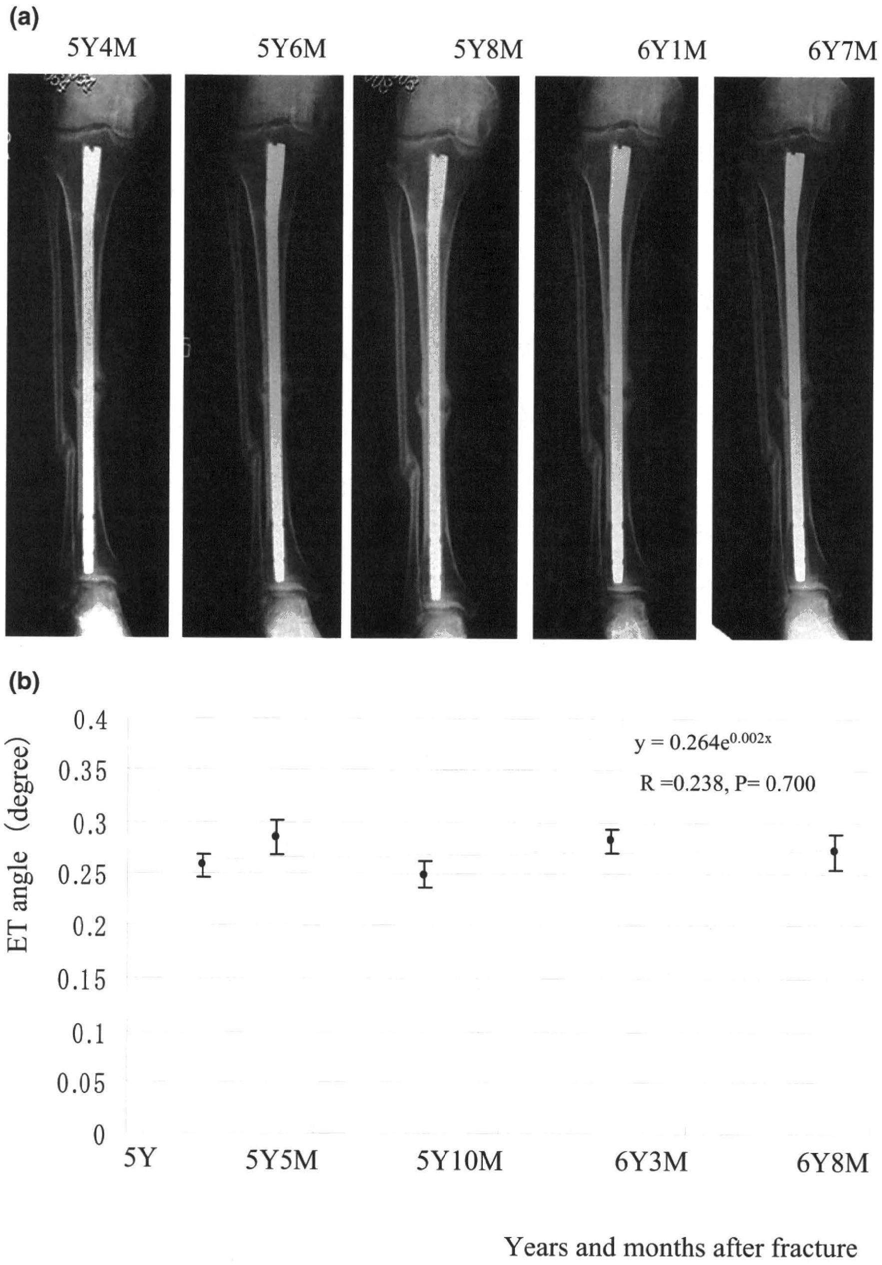

Fig. 6. (a) Time sequential change of the fracture site X-ray from 5 y 4 mo to 6 y 7 mo after fracture in case 7, treated with intramedullary nailing. The X-ray films showed hypertrophic nonunion, but judgment of whether healing was proceeding was extremely difficult. (b) In case 7, the ET angle showed no change over time and the regression lines showed no significant decrease.

cable to patients treated conservatively as well as those managed by surgical intervention with plating or intramedullary nailing.

In this study, the precision and reproducibility of the method were evaluated. The precision of measuring displacement by using the echo tracking system specially designed for bone surface measurement has already been assessed, and a precision of 2.6 μ was demonstrated in our previous study. However, the precision of measuring the bending angle has not been investigated before. We obtained a precision of 0.002°, which was thought to be adequate based on the results of the study by Moorcroft et al. (2001) that evaluated fracture healing. They used the three-point bending test to generate angles of 0.4 to 1.0° in an *in-vivo* measurement trial and connected a goniometer to the bone fragment *via* screw pins fixed to a side bar of the external fixator to detect bending at the fracture site.

When estimation of the linearity of measurement was done in relation to the load, there was excellent

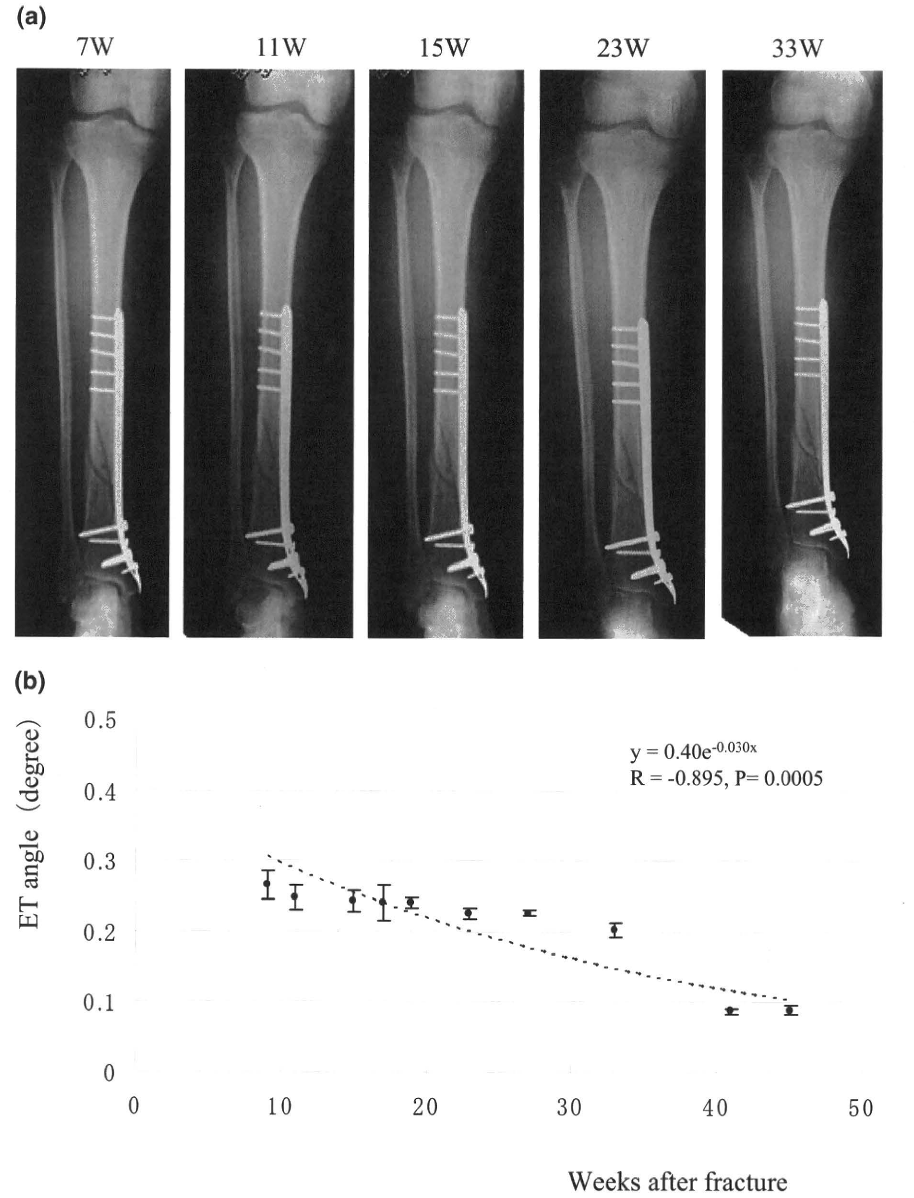

Fig. 7. (a) The X-ray films of case 8, treated with plating. No change of the fracture site or callus was recognized on X-ray films. (b) The ET method measured the bending angle of the plate. The change was very slow, but the angle decreased significantly from 0.28 to 0.2°, and then finally declined to 0.1°.

linearity between magnitude of the load and the ET angle (r = 0.997), indicating that elastic deformation of the fracture site had occurred under a load range of 10 to 30 N. Therefore, measurement was shown to be noninvasive as well as safe, without causing any residual deformity.

Reproducibility of the measurement method was estimated to be 0.015°, which was adequate to evaluate fracture healing quantitatively, because the angle ranged from around 1° in the initial stage to about 0.1° in the final stage when it was almost equivalent to that of the intact tibia. However, we have to improve the reproducibility of measurement *in vivo*. The factors affecting reproducibility *in vivo* include the position of the leg, loading direction and positions of the probes. Among these, the positioning or fixation of the leg seems to have the most influence on the reproducibility of measurement.

For clinical evaluation of fracture healing, data obtained by the ET method were compared with X-ray findings over time. In patients with delayed healing or nonunion, judgment of the healing process using X-ray films was difficult because the direction and conditions of obtaining images were not exactly the same every time, so the findings were not reproducible. In contrast, the echo tracking method evaluated fracture stiffness

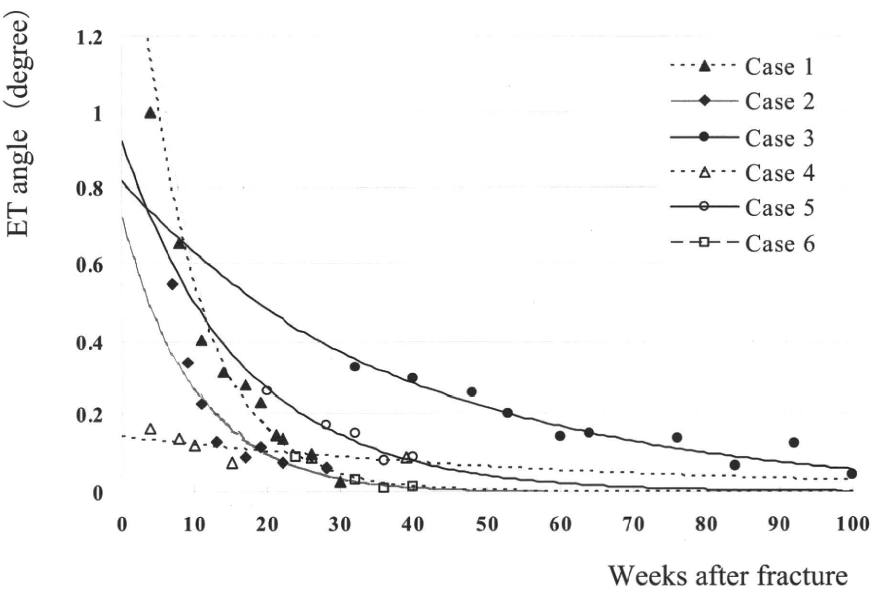

Fig. 8. In cases 1 through 6, the changes of the ET angle showed an exponential pattern. The correlation coefficients obtained by the regression equation for the ET angle and time were very high in these cases.

with considerable accuracy, sensitivity and reproducibility.

In patients with radiographically normal healing, the bending angle decreased exponentially over time. However, in patients with nonunion, the angle remained the same over time. According to the results obtained with previous methods such as the strain gauge method and the invasive method of Jernberger (1970), strain or deformation caused by loading at the healing site has been reported to diminish exponentially over time in patients with normal healing. Among these previous studies, Bourgois and Burny (1972) evaluated fracture healing in hundreds of patients treated with an external fixator that was instrumented with a strain gauge. They not only accumulated considerable clinical data on the strain readings over time, but also theoretically proved by mathematical simulation that the change of the strain over time during normal healing could be expressed as a typical hyperbolic curve. In addition to this, they proved that the time course of the change in strain could also be a hyperbolic curve by developing fracture simulation models with stabilization by intramedullary nailing, plating and external fixation. As a result, their clinical data were compatible with those for the theoretical model of external fixation. They classified the pattern of fracture healing into seven categories depending on the difference in the healing process. Among them, normal healing was defined as healing in which the strain reading *vs.* time curve reaches a plateau at 60 to 90 days after fracture. Slow healing was defined as healing in which the decline of strain was very slow compared with the normal pattern but the healing process was progressive over time. Nonunion was defined as cessation of the progress of healing. In two patients treated with a cast in our study, the ET angle decreased rapidly until 10 weeks after fracture to a level twice that on the intact side, and then it decreased slowly. The exponential regression curve for the echo tracking angle *vs.* time showed a very strong correlation (case 1, $r = -0.975$). Therefore, it can be concluded that the echo tracking method could be used to evaluate normal healing as proposed by Burny et al. (1984). As shown in Fig. 5, the progress of healing in patients treated with intramedullary nailing and bone grafting could be assessed by using the ET method. The ET angle *vs.* time relation in these cases was also expressed by exponential curves. However, the ET angle curve of patient 7 (Fig. 6b) did not show any significant decrease of the angle and there was no correlation between the ET angle and time. From this, the healing process was diagnosed as nonunion. The ET angle of patient 8, treated with plating, showed an extremely slow decrease over time from 9 weeks to 33 weeks, but reduction of the angle was statistically significant until 45 weeks, so the healing process was concluded to be delayed.

Fracture site stiffness was adopted as a parameter for evaluation that was thought to be correlated with strength of bone healing. In various earlier studies of fracture site mechanical properties, stiffness was measured to estimate the strength of the fracture site. However, stiffness is not necessarily correlated with strength. Chehade et al. (1997) investigated this relationship in 24 sheep. The tibia was stabilized with an external fixator and then osteotomy was done. Next, the tibiae were excised at 6, 8 and 10 wk after osteotomy and a 4-point bending test was done. As a result, in the initial stage of healing, stiffness showed a strong correlation with strength ($r = 0.89$), but there was no correlation between them in the remodeling stage. However, as Chehade et al. (1997) stated, because the stiffness of the fracture site is strongly correlated with the strength until remodeling is initiated, it is clinically significant to monitor fracture site stiffness as a substitute for strength to determine the appropriate level of weight bearing so that patients can avoid refracture because of overloading the fracture site during postoperative management. In the remodeling stage, we need to pay special attention to the relationship between stiffness and strength, even if stiffness reached the same value as the intact side.

Fracture healing was evaluated quantitatively by the echo tracking method in patients treated conservatively as well as by internal fixation. All previous methods of assessment could only be applied to patients treated with an external fixator that required the insertion of wires or screw pins, and none of the methods could achieve evaluation in a totally noninvasive manner. The potential problem with evaluating patients treated with internal osteosynthetic devices such as intramedullary nails or plates is that the stiffness at the fracture site is the sum of stiffness for both the healing fracture and the implant. The stiffness of the implant is very high compared with that of the healing fracture because it is made of a metal such as stainless steel or titanium-aluminum-vanadium alloy. Therefore, the combined stiffness at the fracture site is usually very high compared with that in patients receiving conservative treatment by casting. In such patients with internal osteosynthetic devices, comparison of stiffness with the intact side does not have any meaning for evaluation of fracture healing. Therefore, we have to be careful with interpretation of the changes of stiffness over time in such cases. How the implanted material and the configuration of stabilization affect fracture site stiffness should be investigated in the future so that we can assess fracture healing more precisely in patients with internal fixation.

In conclusion, it was demonstrated that the echo tracking method could be clinically applicable to evaluate fracture healing as a versatile, quantitative and noninvasive technique. Further development of this method should be performed so that it can be applied to other anatomical sites by improving accuracy and precision.

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