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NFκBをターゲットとした変形性関節症に対する治療法の開発

冨田哲也* 吉川秀樹

はじめに

本格的な高齢化社会を迎え変形性関節症(osteoarthritis；OA)は増加の一途をたどっている。末期には関節変形と共に疼痛が増悪し，関節機能の著しい低下に伴い日常生活活動能力が障害される。関節軟骨の加齢的影響，力学的ストレスなど様々な因子がその病態に関与していると考えられ，精力的に研究が行われているが，未だその病態は完全には解明されず，有効な保存療法も数少ないのが現状である。近年OAにおいても炎症性サイトカインやmatrix metalloproteinase(MMPs)の産生がその病態の進行に重要な役割を果たしていることが明らかにされ，関節局所でこれらの因子をコントロールする必要性が提唱されている[1]。その中で転写調節因子nuclear factor κB(NFκB)が重要な治療上のターゲットとして考えられている[2]。NFκBは不活化の状態ではその制御抑制因子IκBと複合体を形成し核外に存在するが，活性化刺激によりIκBがリン酸化され，NFκBが核内へ移行し標的遺伝子の発現を活性化する。

NFκBデコイ型核酸医薬

われわれは1990年代後半より転写調節因子レベルでの制御を目的としたデコイ型核酸医薬による治療法を考案し研究してきた。デコイとは元来“おとり”という意味で，特定の転写調節因子の結合部位の結合を阻害し，活性化される遺伝子群の発現抑制あるいは発現増強を行うものである。そのため転写調節因子の結合部位を含む短いオリゴヌクレオチドを合成し，二重鎖核酸にしたのち細胞内へ導入する。そのメカニズムは明らかであり，転写調節因子の結合部位への結合阻害によるプロモーター活性の低下である。これまでに炎症性関節炎モデル，ヒト関節リウマチ滑膜細胞等での有効性を明らかにしてきた[3][4]。今回前十字靱帯切除変形性関節症モデルラットを用いた検討では，6回連続で膝関節内にnaked NFκBデコイ型核酸医薬を局所投与したところ，組織学的に関節軟骨の変性の進行が有意に抑制された。関節軟骨の変性進行に重要な役割を果たすと考えられている炎症性サイトカイン(IL-1β，TNFα)の発現は，naked NFκBデコイ型核酸医薬投与群でPBSあるいはscrambledデコイ型核酸医薬投与群に比べ，関節軟骨中および滑膜中で有意に抑制されていた。本実験では関節内局所投与されたNFκBデコイ型核酸医薬の大部分が関節滑膜に導入されていたことを考慮すると，関節軟骨中での炎症性サイトカイン発現レベルの低下は滑膜よりのこれらサイトカイン発現コントロールによる二次的な影響と考えられた。現時点ではin vivoでは正常軟骨組織にはベクター無しでは，高い導入効率は期待できず，より変性初期の関節軟骨細胞をターゲットにするには，導入方法について検討が必要である。一方変性軟骨細胞にはnakedでもある程度導入可能であり現在その効果を検討中である。次いでヒト関節軟骨細胞を用いた三次元培養にIL-1βを添加した系での，NFκBデコイ型核酸医薬の影響を検討した。この系ではIL-1β添加によりNFκBが活性化することがすでに証明されている。NFκBデコイ型核酸医薬添加によりヒト培養軟骨細胞中のIL-1βおよびMMP-1の遺伝子レベルでの発現は有意に抑制された。また細胞基質の産生はIL-1β添加により有意に低下していたが，NFκBデコイ型核酸医薬添加によりその産生量は正常軟骨細胞のレベルに回復した。これらの結果よりヒト関節軟骨細胞に対してもNFκBデコイ型核酸医薬は有効であることが示唆された。

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図1 NFκBデコイ型核酸医薬の作用機序
NFκBデコイはその特定の結合部位に競合的に結合し，NFκBの結合阻害によるプロモーター活性の低下を生じさせ，その下流に存在する遺伝子発現を制御する。

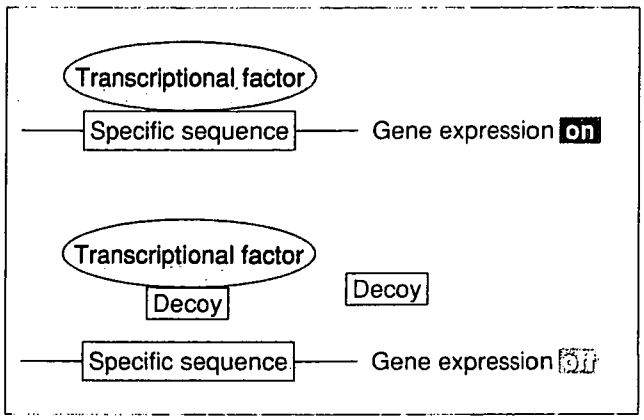
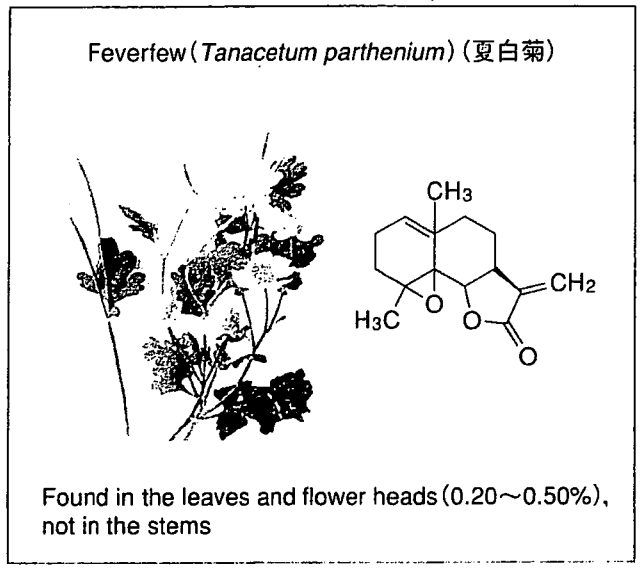


図2 Parthenolideの構造



Parthenolide

Parthenolideは古来偏頭痛に効果があるとされているハーブの一種であるfeverfew(夏白菊)より抽出合成された低分子化合物で，抗炎症作用を持つことが知られている。近年その作用機序がNFκBの結合抑制であることが示された。当教室の岸田ら[5]はマウス骨肉腫細胞の肺転移をparthenolideがNFκBのdown regulationにより抑制することを証明した。われわれはparthenolideの炎症性関節炎やOAの治療補助としてのポテンシャルを検討している。parthenolideを上記のヒト関節軟骨三次元培養にIL-1βを添加した系で検討したところ，軟骨細胞中のIL-1βおよびMMP-1,-3の遺伝子レベルでの発現は有意に抑制された。現在in vivoでの効果を検討中である。

治療上のターッゲトとしてのNFκB

NFκBが様々な疾患でその病態形成に重要な役割を果たしていることは明らかにされている。また近年の分子生物学的手法により様々なNFκBの阻害ステップや阻害剤が報告されている。しかし現時点ではまだ臨床の場に応用されたものはなく，今後ヒトへの臨床応用という観点よりの安全性，有効性等の十二分な検討が必要である。この点においてはすでに他疾患でヒトへの投与が行われているデコイ型核酸医薬と共にparthenolideのような低分子化合物は臨床応用が期待される。一方OAの病態という観点からは，より本体的な病的ターゲットが明らかになり，その治療法が開発されることが当然望まれるが，それまで手をこまねいているのではなく，少しでもOAの進行に対し抑制効果が期待できるのであれば，NFκBをターゲットにした治療法を開発する意義はあると考えられる。

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医工連携による次世代人工骨・人工関節の開発

研究ノート

吉川秀樹*

Development of new bone substitute and prosthesis by medicine-engineering cooperation

Key Words：Bone, Substitute, Prosthesis, hydroxyapatite

骨組織は，骨折の治癒現象に代表されるように，本来豊かな再生能力を有している．しかし，骨腫瘍の切除後や，重度の粉砕骨折などで生じた大きな骨欠損に対しては，自家骨では対応できず，人工骨を用いた骨の再生医療が必要となる．また，人口の高齢化に伴い，変形性関節症が増加し，人工関節の置換を余儀なくされる患者さんが増加しつつある．しかし，現在の人工関節では長期の耐久性には未だ問題があり，しばしば再置換術が必要となる．骨は力学的強度を必要とする組織であり，骨・関節の再生／修復には，骨との結合が良好な人工骨と，骨と親和性のある新しい人工関節の開発が必要である．

連通多孔体人工骨の開発

人工骨は，1）移植骨採取の侵襲がない，2）任意の量，形状を調節できる．3）生体との適合性がよい，4）免疫反応がないなどの利点を有するが，一方では，1）力学的強度が弱い，2）骨細胞の侵入が困難である，3）高価であるなどの問題点も有している．今日まで人工骨として，アルミナ，ジルコニア，バイオグラス，ハイドロキシアパタイトなど様々な素材が使用されてきた．中でも，ハイドロキシアパタイトはヒトの骨の無機質成分に近く，その優れた生体親和性，骨伝導能から人工骨として最も適していると考えられる．しかし，既存のハイドロキシアパタイトは，気孔と気孔が組織侵入に十分

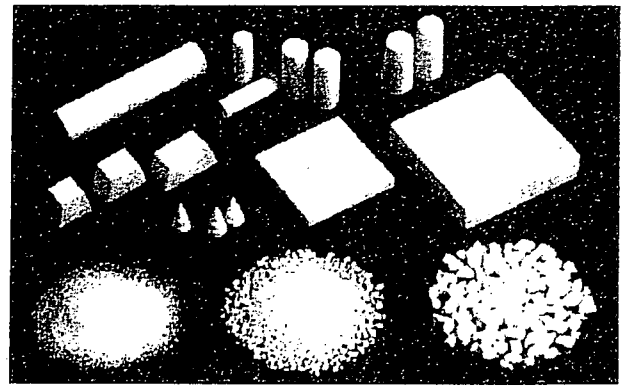

図1　骨再生のための新規人工骨（NEOBONE）

なサイズの連通孔でつながっておらず，内部まで骨形成は期待できなかった．一方，従来の製法で連孔構造を求めると，細胞の侵入は良好であるが，2-3 Mpa程度の力学的強度に劣る人工骨となり，臨床使用には適さない．著者らは，力学的強度を有し，かつ骨細胞や骨増殖因子の導入が可能な骨補填材料として，気孔間連通構造を有する新規ハイドロキシアパタイトを開発した（図1）．“起泡ゲル化技術”による新規多孔体ハイドロキシアパタイト（NEOBONE）は，ほぼ球形で比較的均一のサイズの気孔が秩序良く配列し，ほぼ全気孔が気孔間連通孔で連絡している（図2左）．連通孔径分布は10-80 μm（平均40 μm）にあり，気孔の90%が細胞や組織が十分通過できる大きさの連通孔でつながっており，気孔の内部に骨髄幹細胞，血管，BMPなどの

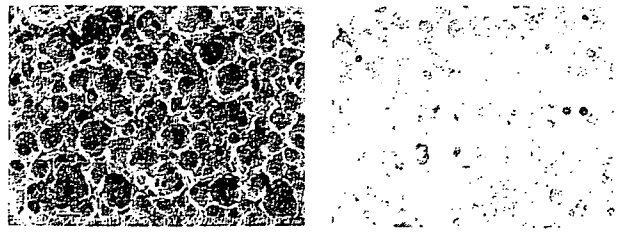

図2　左：NEOBONEの内部微細構造（走査電顕像）
右：ウサギ大腿骨に移植後6週の組織像

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増殖因子／サイトカインや遺伝子の導入が可能である．力学的強度は初期圧縮強度で12Mpaであり優れた数値を示した．ウサギ大腿骨にNEOBONEを移植した際に，移植後わずか6週間で直径6mmの円柱の深層にまで気孔間連通孔を経て，豊富な血管新生を伴う，新生骨，新生骨髄が観察され，優れた骨再生能を示した（図2右）．また，この骨新生に伴い圧縮強度は移植後9週で初期強度の3倍に達した．2003年9月に，薬事認可を受け，臨床使用が可能となり，関節リウマチ，骨粗鬆症，骨腫瘍，骨折などの骨欠損部に使用されている．医療材料として発売後も副作用を示さず，術後3～6ヶ月で良好な骨形成を認めた（図3）．今回開発した新規多孔体ハイドロキシアパタイトは気孔間連通構造を有するため，容易に中心部まで血管・骨組織が侵入すること，今後の増殖因子や細胞の導入にも有用であることから，骨組織の再生医療のための優れた担体と考えられた1）．

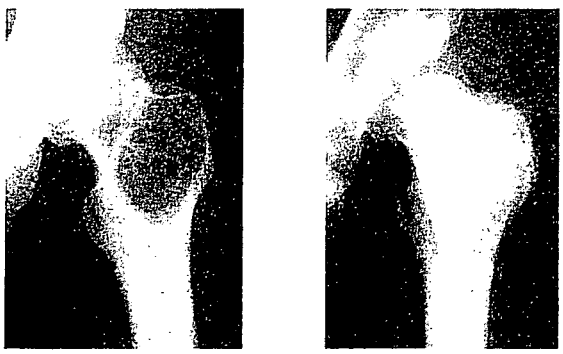

図3　左：17才，男子，大腿骨骨巨細胞腫（術前）
右：術後3ヶ月での骨形成

レーザー微細加工技術を用いた人工関節の開発

人工関節手術は，変形性関節症や関節リウマチにより関節機能を失った患者さんに対する機能再建法として大きく貢献してきた．しかし，高齢化社会では，人工関節の寿命が重大な問題となりつつある．なかでも最大の問題点は，人工関節の金属と骨組織の間で生じるゆるみである．ゆるみにより，臨床的には痛みを生じ，歩行困難となり，最終的には再人工関節置換手術を余儀なくされる．金属／骨の十分な固着力を得るには，1960年代より，骨セメントによる接着が行われてきた．しかし，再手術時の除去の困難さ，細胞毒性の問題等から，近年では，直接金属に金属粒子やハイドロキシアパタイトを噴霧し

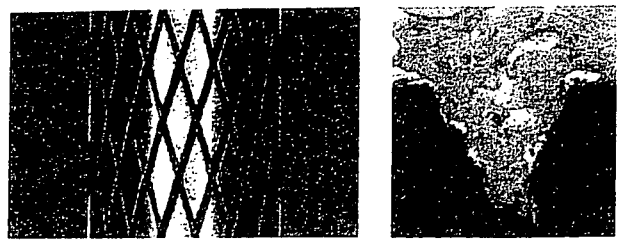

図4　左：レーザーによる金属表面微細加工
右：ウサギ大腿骨に移植後4週の組織像

て，表面に凹凸を作り臨床使用されてきた．しかし，微粒子の剥離や，均一な表面形状の制御が困難であることなど問題点を残してきた．著者らは，レーザーによる微細表面加工技術を用い，CoCr合金，Ti合金などの金属表面にコンピューター制御により溝構造を作成し，骨組織との固着力をさらに強化することを試みた．金属円柱片（直径: 5mm，長さ: 15mm）を作成し，表面にYAGレーザーによって格子状の溝形状を作成した（溝幅：500μm，深さ500μm）（図4左）．溝の交差角度は70度，溝間隔は3mmであった．対照群として現在臨床使用されている手法で金属サンプル表面にポーラスコーティングしたものを用い，各サンプルをウサギの大腿骨顆部に挿入設置した．術後4週での組織学的検討では，溝の深部まで良好な骨形成を認めた（図4右）．さらに金属骨間力学的固着強度評価を押し抜き強度実験で行った．ウサギ大腿骨内に挿入した金属片を大腿骨ごと術後4週で摘出し，島津社製（EHF-F01）マテリアルテスティングマシーンを用いて金属を5mm/分の速さで押し，金属と骨との間に動きが生じた瞬間の力を計測した．その結果，従来のポーラスコーティング法より約2倍の固着力を獲得した2）．また，このレーザーによる溝加工はコンピューター制御により任意の溝幅，溝深さ，溝パターンを

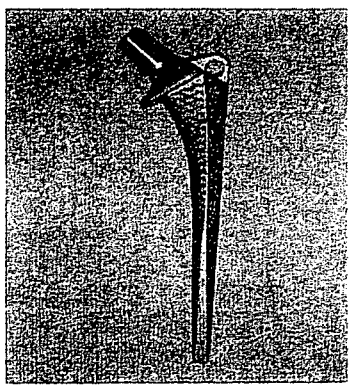

図5　レーザー表面加工人工股関節（ヒト用試作品）

決定できるため，最適な骨組織の侵入条件や強度を決定することが可能である．本技術は，コーティングではなく人工関節自体への加工という全く新しい製造概念であり，異物を添加しない人体に親和性のある人工関節として，臨床応用が期待される．現在，ヒト用試作品を作成し，強度試験などの前臨床試験を行っている（図5）．

今回開発した，人工骨，人工関節は，いずれも単一の素材からなり，骨組織との親和性も高く，人体にやさしい医療材料と考えることができる．これら骨再生，骨との固着性に優れた医療材料の臨床使用により，早期の骨再生，長期の耐久性が得られ，骨関節疾患の術後早期社会復帰，寝たきり老人の減少などが期待できる．医療費の削減に結びつくだけでなく，生体材料産業の活性化，人工臓器産業の開拓などにより大きな経済効果があると考える．

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ORIGINAL ARTICLE

Hideki Tsuboi · Akihide Nampei · Yoshito Matsui
Jun Hashimoto · Shinichi Kawai · Takahiro Ochi
Hideki Yoshikawa

Celecoxib prevents juxta-articular osteopenia and growth plate destruction adjacent to inflamed joints in rats with collagen-induced arthritis

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Abstract The effect of celecoxib, a selective cyclooxygenase-2 inhibitor, on juxta-articular osteopenia and growth plate destruction adjacent to inflamed joints was investigated in rats with collagen-induced arthritis. Forty rats were assigned to the following six groups: (1) an untreated arthritis group; (2–5) arthritis rats receiving indomethacin (3 mg/kg per day), dexamethasone (0.2 mg/kg per day), or celecoxib (5 or 50 mg/kg per day), and (6) normal control rats. Drugs were administered for 2 weeks from the onset of arthritis. Then the hind paws were measured. Juxta-articular osteopenia and growth plate destruction adjacent to inflamed joints were also assessed using plain radiography, bone mineral density measurement, histology, and histomorphometry. Each treatment reduced inflammation, but only dexamethasone and high-dose celecoxib prevented bone loss adjacent to inflamed joints and significantly decreased bone resorption. In contrast, no treatment affected bone formation parameters. Growth plate destruction adjacent to inflamed joints was prevented by indomethacin, dexamethasone, and high-dose celecoxib. Although dexamethasone abolished inflammation, growth plate destruction was still observed. In conclusion, among the various drugs tested, only celecoxib had a preventive effect on both growth plate destruction and bone loss adjacent to inflamed joints in this arthritis model.

Key words Celecoxib · Growth plate destruction · Juvenile idiopathic arthritis · Juxta-articular osteopenia · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by synovitis associated with the progressive destruction of cartilage and bone,[1,2] including juxta-articular osteopenia adjacent to inflamed joints and focal erosion of the subchondral bone and joint margins.[3] Recent studies have suggested that both proliferating synovial cells and bone-resorbing osteoclasts play an important role in the bone resorption that occurs at these sites. Juvenile idiopathic arthritis (JIA) is another chronic inflammatory disease that is characterized by arthritis associated with progressive destruction of cartilage and bone that leads to abnormal growth of juxta-articular epiphyses, resulting in joint malalignment and destruction, extremities of different lengths, and short stature.[4]

Nonsteroidal anti-inflammatory drugs (NSAIDs), including indomethacin, are effective anti-inflammatory and analgesic agents that are commonly used to treat RA and JIA, and these drugs decrease the production of prostaglandins (PGs) by direct inhibition of the activity of cyclooxygenase (COX).[5,6] Prostaglandins (PGs) are important inflammatory mediators that are produced at sites of inflammation, including the joints of patients with RA and JIA. Prostaglandins enhance or prolong the effects of various proinflammatory agents and thus aggravate inflammation. Prostaglandins are produced from arachidonic acid by COX,[7,8] and two isoforms of COX are known to exist, which are COX-1 that is constitutively expressed by various cells and tissues[9] and COX-2 that is expressed by inflammatory cells in response to various stimuli.[10]

Previous studies on inflammatory bone conditions have showed that osteoblasts or stromal cells overexpress COX-2, which produces PGs that promote bone resorption. It was also reported that genetically COX-2-deficient mice show impaired bone resorption in response to parathyroid hormone or 1,25-hydroxyvitamin D_3. These findings suggest that COX-2 may have an important role in bone resorption as well as in inflammation, which could be quite distinct from that of COX-1.[11–13]

Selective COX-2 inhibitors are becoming more widely used to treat RA and JIA.[14] These drugs are known to reduce PG production. In addition, celecoxib (a selective COX-2 inhibitor) has been reported to have several effects on bone. Kawaguchi et al.[15] found that COX-2 inhibitors suppress osteoclastogenesis, while Igarashi et al.[16] showed that celecoxib suppresses both bone resorption and osteoclastogenesis in vitro. In addition, Katagiri et al.[17] recently reported that selective COX-2 inhibitors can reduce pannus expansion and joint erosion in a rat model of arthritis. Moreover, Mastbergen et al.[18] reported that celecoxib prevented cartilage damage induced by proinflammatory cytokines in an organ culture system.

These reports have raised the possibility that selective COX-2 inhibitors could prevent juxta-articular osteopenia and growth plate destruction in RA or JIA. Therefore, we investigated the effect of the selective COX-2 inhibitor celecoxib on juxta-articular osteopenia and growth plate destruction in rats with collagen-induced arthritis (CIA), which are commonly used as a model of inflammatory arthritis like RA and develop juxta-articular osteopenia[19] as well as early closure of the juxta-articular growth plates.[20]

Materials and methods

Collagen-induced arthritis model

Collagen-induced arthritis was induced in 6-week-old female Lewis rats (Clea Japan, Tokyo, Japan) using a modification of the method described previously.[21] Rats were anesthetized and immunized intradermally with 0.5 mg of bovine type II collagen (Cosmo Bio, Tokyo, Japan) that had been emulsified in 0.5 ml of Freund's incomplete adjuvant (Difco, Detroit, MI, USA) at 4°C. On day 7, the rats received an intradermal booster injection, which was half the volume of the first dose. The onset of arthritis in the ankle joints could usually be recognized between days 14 and 16, and animals without obvious arthritis by day 16 were excluded from this study. The incidence of arthritis was 70.0% (30 of 43 rats). On day 17, the hind paw volume of each rat was measured with a TK-101 CMP Plethysmometer (Muromachi Machine, Tokyo, Japan), and animals with a hind paw volume greater than 1.65 ml were randomized in equal numbers ($n = 5$ each) to the following five groups: (1) an untreated CIA control group, (2) a group treated with indomethacin at 3 mg/kg per day, (3) a group treated with dexamethasone at 0.2 mg/kg per day, (4) a group treated with celecoxib at 5 mg/kg per day (cele.5), and (5) a group treated with celecoxib at 50 mg/kg per day (cele.50). Five nonimmunized normal control rats were also studied according to the same experimental protocol. All present animal experiments were approved by the institutional review board of Osaka University Graduate School of Medicine.

Drug treatment

Celecoxib was a kind gift from Pharmacia (Skokie, IL, USA), while dexamethasone and indomethacin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Drugs were prepared as suspensions in 0.5% methylcellulose (Wako, Tokyo, Japan). Rats were treated orally once a day for 2 weeks at the above-mentioned doses with a dosing volume of 0.5 ml/day. Administration was begun on day 17 of the study and continued until the final assessment on day 30.

Radiographic evaluation

On day 30, all rats underwent radiography. After being killed with an overdose of ketamine intramuscularly, the lower extremities were resected and the bones were cleaned of adherent tissue. Then the limbs were positioned over a cassette containing X-ray film (Eastman-Kodak, Seattle, WA, USA) and radiographs were obtained with a conventional microradiography unit (M-60, Softex, Tokyo, Japan) at 30 kV and 3 mA for 75 s.

Measurement of bone mineral density (BMD)

The BMD of the proximal one-third of the tibia was measured by a bone densitometer (Lunar PIXImus; Lunar, Madison, WI, USA) using software provided with the instrument. The region-of-interest (ROI) tool was employed to identify the proximal tibia. To eliminate the fibula from the scans, the oval exclusion ROI was positioned over this bone (Fig. 3Aa).[22] All BMD analyses were done by the same investigator (H.T.).

Bone histomorphometry

All rats underwent double fluorescent labeling before being euthanized. On days 23 and 27, tetracycline hydrochloride (20 mg/kg; Sigma) were injected intraperitoneally. Bone specimens were fixed in 70% ethanol, prestained in Villanueva bone stained for 72 h, dehydrated in alcohol and acetone, and embedded in methylmethacrylate. Then the proximal tibia was cut into 5-μm thick frontal sections for histomorphometry of cancellous bone.[23] Measurements were performed at a magnification of ×320 in the secondary spongiosa at 1 mm from the growth plate using Bone Histomorphometric System software (System Supply, Nagano, Japan). The histomorphometric parameters employed in this study were derived from Parfitt et al., and have been approved by an American Society for Bone and Mineral Research (ASBMR) committee.[24] As static parameters, the trabecular bone volume (BV/TV) and trabecular thickness (Tb.Th) were measured. To measure bone formation, the osteoid surface relative to bone surface and the osteoblast surface relative to bone surface were calculated (OS/BS and Ob.S/BS, respectively). To assess bone resorption, the eroded surface and osteoclast surface were quantified

relative to the bone surface (ES/BS and Oc.S/BS, respectively). To determine the effect of each drug on growth plate destruction, the width of the growth plate and the number of osteoclasts relative to the bone surface (N.Oc/BS) were measured.

Statistical analysis

Results are presented as the mean ± SD. Differences were analyzed by using analysis of variance, and $P < 0.05$ was considered to indicate statistical significance.

Results

Hind paw volume

The hind paw volume of the rats was measured with a TK-101 CMP Plethysmometer at weekly intervals. On days 24 and 30, the hind paw volume of drug-treated animals was significantly smaller than that of the untreated CIA control group (Fig. 1).

Juxta-articular osteopenia

Radiography of the knee joint showed that juxta-articular osteopenia was very mild in the cele.50 or dexamethasone groups, while severe juxta-articular osteopenia was seen in the untreated CIA, indomethacin, and cele.5 groups (Fig. 2).

Quantitative evaluation of juxta-articular osteopenia by measuring the BMD of the proximal one-third of the tibia (Fig. 3Aa) showed that BMD was significantly higher in the cele.50 group (mean ± SD: 0.183 ± 0.02 g/cm^2) and the dexamethasone group (0.247 ± 0.09 g/cm^2) than in the untreated CIA rats (0.155 ± 0.05 g/cm^2). However, there was no significant difference of BMD between the indomethacin group (0.155 ± 0.01 g/cm^2) or the cele.5 group (0.166 ± 0.02 g/cm^2) and the untreated CIA rats (0.155 ± 0.05 g/cm^2) (Fig. 3Ab). Histomorphometric analysis gave results consistent with the BMD data because decrease of BV/TV and Tb.Th were significantly suppressed in the cele.50 group (13.6% ± 3.15% and 48.1 ± 5.43 μm, respectively) and the dexamethasone group (22.8% ± 6.43% and 56.9 ± 4.56 μm) than in the untreated CIA group (5.32% ± 1.53% and 34.0 ± 5.14 μm). This protective effect of high-dose celecoxib and dexamethasone against bone loss in CIA rats was accompanied by a significant decrease of ES/BS (cele.50 and dexamethasone: 20.6% ± 6.37% and 11.6% ± 3.33%, respectively) and Oc.S/BS (6.92% ± 3.02% and 3.43% ± 1.39%), which are bone resorption parameters, compared with the untreated CIA group (ES/BS 39.4% ± 4.94% and Oc.S/BS 13.5% ± 5.40%). However, there were no significant changes of bone formation parameters (OS/BS and Ob.S/BS were respectively 28.3% ± 17.2% and 19.7% ± 15.5% for cele.50, 30.4% ± 5.93% and 16.4% ± 3.36% for dexamethasone, and 27.2% ± 12.3% and 17.9% ± 10.8% for untreated CIA). On the other hand, there were no significant differences of any parameters between the indomethacin group (BV/TV, Tb.Th, ES/BS, Oc.S/BS, OS/BS, and Ob.S/BS were 6.64% ± 0.636%, 33.1% ± 1.38 μm, 44.4% ± 0.226%, 18.2% ± 0.58%, 13.4%

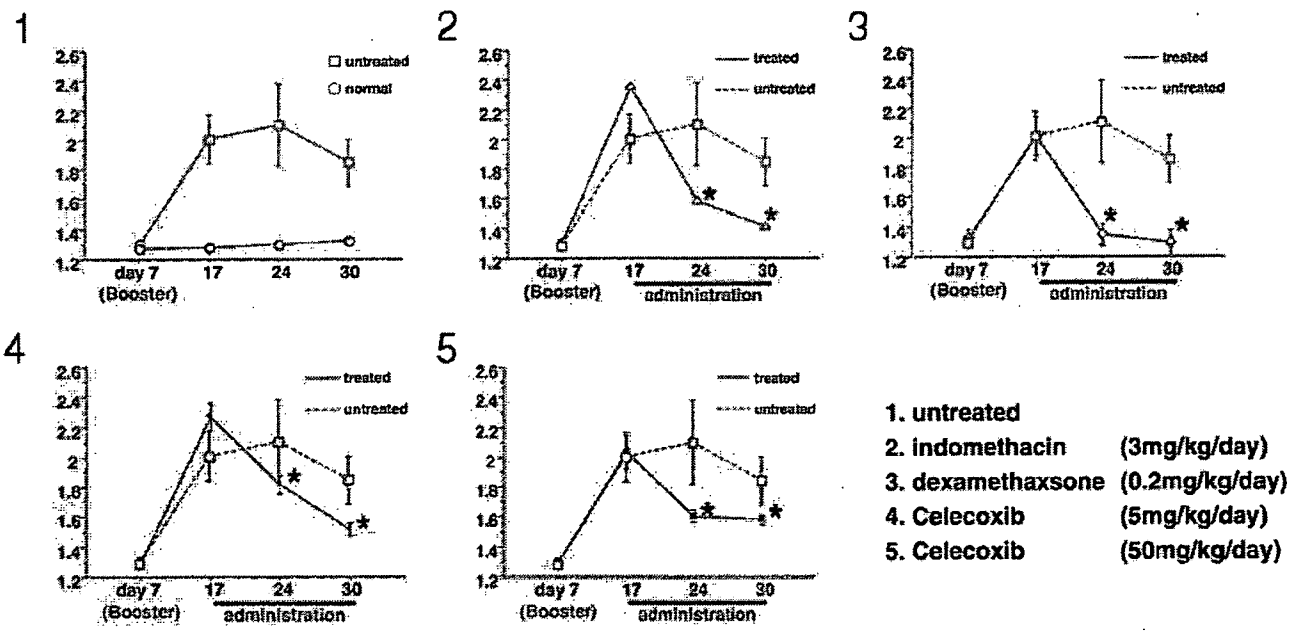

Fig. 1. Effect on the hind paw volume. Each drug significantly improved collagen-induced arthritis (CIA), as evaluated by hind paw volume. Data from five rats in each group were presented as the mean ± SD. *1*, untreated CIA group; *2*, indomethacin group; *3*, dexamethasone group; *4*, cele.5 group; *5*, cele.50 group; *6*, normal control group. On days 24 and 30, the footpad volume in groups 2, 3, 4 and 5 was significantly smaller than in the untreated CIA control group (1). *$P < 0.01$ for the untreated CIA control group vs. each treated group (analysis of variance; ANOVA)

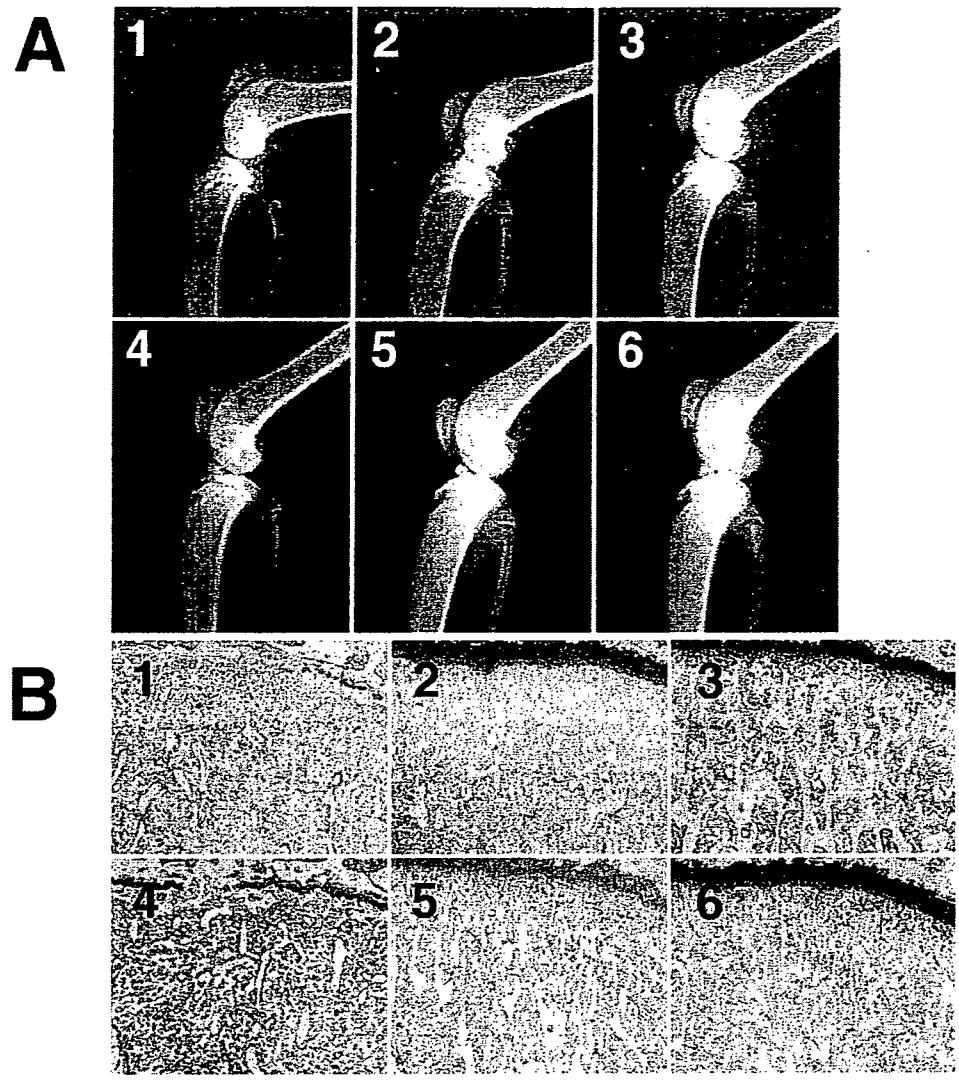

Fig. 2A,B. Effect on juxta-articular osteopenia. **A** Radiographic findings. Representative images selected from the five rats (ten limbs) in each group are presented. *1*, untreated CIA group; *2*, indomethacin group; *3*, dexamethasone group; *4*, cele.5 group; *5*, cele.50 group; *6*, normal control group. Rats from the cele.50 group (5) and the dexamethasone group (3) showed denser juxta-articular bone than untreated CIA rats (1) or rats from the indomethacin group (2) or the cele.5 group (4). An X-ray image of a nonimmunized normal control rat is also shown (6). **B** Histological villanueva bone stained findings. Representative images from the five rats (ten specimens) in each experimental group are presented. Specimens from the untreated CIA group (*1*), the indomethacin group (*2*), and the cele.5 group (*4*) reveal marked loss of bone trabeculae at the proximal tibial epiphysis, as well as the metaphysic, when compared with the nonimmunized normal control rats (*6*). In the cele.50 group (*5*) and the dexamethasone group (*3*), trabeculae are also decreased compared with the non-immunized normal control group (*6*), but are preserved to a certain extent. Original magnification ×40

± 5.43%, and 8.61% ± 5.16%, respectively) or the cele.5 group (6.48% ± 0.757%, 37.0 ± 1.68μm, 40.3% ± 6.24%, 19.1% ± 6.27%, 24.7% ± 9.21%, and 14.4% ± 9.69%) and the untreated CIA rats. Bone histomorphometry revealed the following values in normal control rats. BV/TV, Tb.Th, ES/BS, Oc.S/BS, OS/BS, and Ob.S/BS were 28.3% ± 3.46%, 55.9 ± 4.65μm, 29.7% ± 3.00%, 12.5% ± 1.01%, 31.1% ± 5.9%, and 22.2% ± 5.21%, respectively.

Growth plate thickness

Histological examination showed that the growth plate was almost completely preserved in the indomethacin and cele.50 groups, and was partially preserved in the dexamethasone group. In contrast, the growth plate had disappeared in the untreated CIA rats (Fig. 4A, B). Quantitative evaluation of the width of the growth plate showed no significant difference between normal control rats (129 ± 10.7mm) and the indomethacin group (126 ± 14.1mm) or the cele.50 group (136 ± 47.7mm). However, a significant difference was noted between normal rats and the dexamethasone group (61.9 ± 10.0mm), the cele.5 group (15.2 ± 4.64mm), and the untreated CIA group (16.1 ± 15.2mm). The value of N.Oc/BS before administration (on day 17) and in the untreated, indomethacin, dexamethasone, cele.5, and cele.50 groups was 3.21 ± 0.636no./mm, 2.79 ± 0.636no./mm, 3.74 ± 0.87no./mm, 0.640 ± 0.256no./mm, 4.96 ± 1.92no./mm, and 1.02 ± 0.694no./mm, respectively. N.Oc/BS showed a significant difference between before administration (day 17) and the values obtained in the dexamethasone group and the cele.50 group.

Discussion

In this study, we demonstrated an anti-inflammatory effect of high-dose celecoxib (50mg/kg per day), as well as an inhibitory effect on juxta-articular osteopenia, which was mainly due to decreased bone resorption according to the histomorphometric findings. High-dose celecoxib also pre-

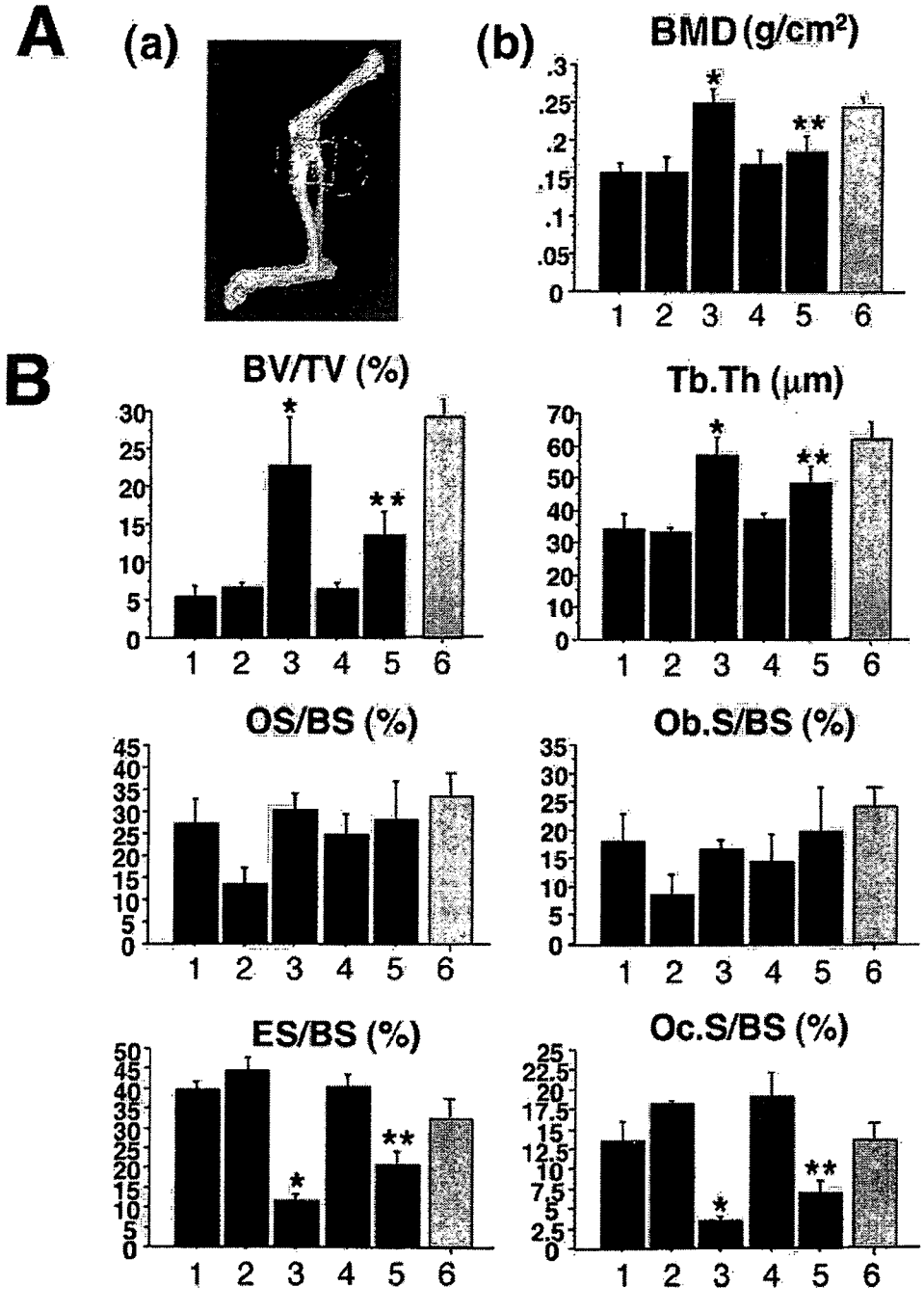

Fig. 3A,B. Effect on the bone mineral density (*BMD*) and histomorphometric parameters. **A** BMD analysis. (**a**) The BMD of the proximal one-third of tibia was measured by a bone densitometer using special software provided by the manufacturer. The region-of-interest tool was employed to define the proximal tibia and to eliminate the fibula from the scans. (**b**) Data are shown as the mean ± SD for five rats in each experimental group: *1*, untreated CIA group; *2*, indomethacin group; *3*, dexamethasone group; *4*, cele.5 group; *5*, cele.50 group; *6*, normal control group. $^{*}P < 0.01$, $^{**}P < 0.05$ for the untreated CIA group vs the dexamethasone and cele.50 groups, respectively (ANOVA). **B** Histomorphometric analysis. *1*, untreated CIA group; *2*, indomethacin group; *3*, dexamethasone group; *4*, cele.5 group; *5*, cele.50 group; *6*, normal control group. Both BV/TV and Tb.Th were significantly preserved in the cele.50 group (*5*) and the dexamethasone group (*3*). $^{*}P < 0.01$, $^{**}P < 0.05$ for the untreated CIA group vs the dexamethasone group and cele.50 group, respectively (ANOVA). *BV/TV*, trabecular bone volume; *Tb.Th*, trabecular thickness; *OS/BS*, osteoid surface relative to bone surface; *Ob.S/BS*, osteoblast surface relative to bone surface; *ES/BS*, eroded surface quantified relative to the bone surface; *Oc.S/BS*, osteoclast surface quantified relative to the bone surface

vented the growth plate destruction that usually occurs in CIA. In contrast, low-dose celecoxib (5 mg/kg per day) did not demonstrate a preventive effect on juxta-articular osteopenia or growth plate destruction, although it still reduced inflammation. These findings suggest that celecoxib may have different actions at high doses from those seen at low doses. The low dose of celecoxib used in this study is similar to the clinical dosage for RA patients and there have been no previous reports about the improvement of juxta-articular osteopenia and growth plate destruction by celecoxib in either the experimental or clinical setting. Therefore, further investigations will be necessary to better define this anti-osteoporotic effect of celecoxib, including studies on juxta-articular osteopenia and growth plate destruction in patients with RA and JIA.

Animals with CIA, including rats and mice, are commonly used to investigate the pathology of inflammatory arthritides such as RA or to confirm the effects of anti-inflammatory drugs. Previously, Bogoch et al.[19] reported the occurrence of juxta-articular bone loss in rabbits with experimental inflammatory arthritis. Hanyu et al.[25] concluded that the cause of juxta-articular osteopenia in CIA rats was a significant increase of osteoclasts along with a decrease in the rate of bone formation based on their histomorphomet-

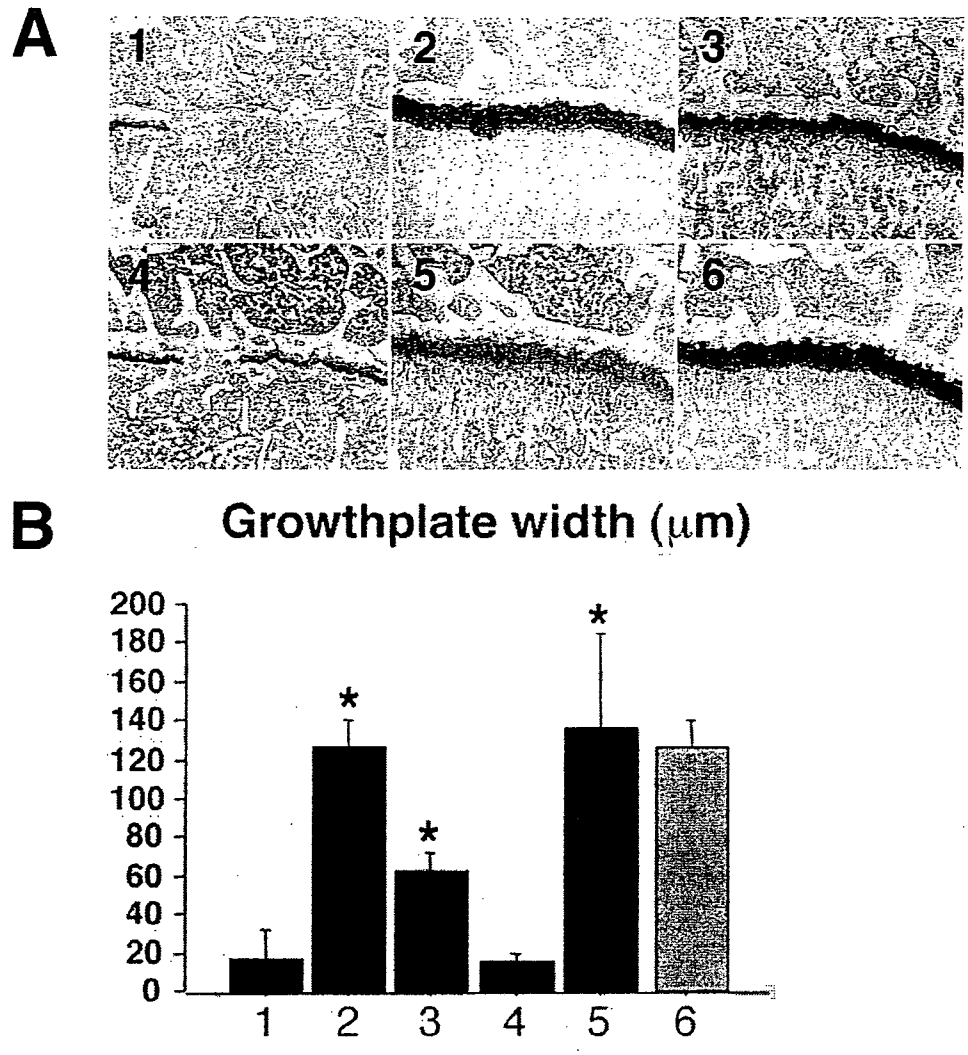

Fig. 4A,B. Effect on growth plate destruction. **A** Histological findings in the *1*, untreated CIA group; *2*, indomethacin group; *3*, dexamethasone group; *4*, cele.5 group; *5*, cele.50 group; *6*, normal control group. **B** Growth plate width. Measurement of the proximal tibial growth plate showed that it was significantly wider in the indomethacin, dexamethasone, and cele.50 groups than in the untreated CIA group or cele.5 group. Both indomethacin and high-dose celecoxib were more effective than dexamethasone. *$P < 0.01$ for untreated CIA group vs the indomethacin, dexamethasone, and cele.50 groups (ANOVA)

ric analysis. Juxta-articular osteopenia is a typical finding in RA patients, and osteoclasts are often observed in the juxta-articular region on histological examination.[1,26-30] Accordingly, osteoclasts are thought to play an important role in the occurrence of juxta-articular osteopenia in patients with RA, especially when there is rapid bone erosion. Hanyu et al.[25] also reported a decrease in the rate of bone formation in CIA rats. Our histomorphometric analysis demonstrated that the protective effect of high-dose celecoxib against bone loss in CIA rats was associated with a significant decrease of bone resorption by osteoclasts. However, high-dose celecoxib could not ameliorate the decrease of bone formation parameters in CIA, indicating that decreased bone resorption by osteoclasts may be the major action by which high-dose celecoxib prevents bone loss.

Recently, high-dose celecoxib was reported to induce apoptosis of cancer cells, stromal cells, and rheumatoid synovial fibroblasts, although low doses do not have an apoptogenic effect.[31-35] This was an unexpected finding for a COX-2 inhibitor, and it seems to be a specific action of celecoxib alone.[31-35] Accordingly, osteoclastogenesis in the juxta-articular region might have been suppressed by decreased RANKL expression on fibroblasts or stromal cells, which is essential for osteoclastogenesis to occur,[26-30] through both the inhibition of PG production and an apoptotic effect on these cells. Therefore, juxta-articular osteopenia may have been improved by a decrease of osteoclasts as our bone histomorphometric analysis showed. Furthermore, our data suggest that high-dose celecoxib may not only prevent inflammation but also juxta-articular osteopenia in patients with RA.

Although low-dose celecoxib and indomethacin had an excellent anti-inflammatory effect, neither agent improved juxta-articular osteopenia in CIA rats. Thus, the low dose of celecoxib and the dose of indomethacin that we tested (a common clinical dose) may have been insufficient to inhibit osteoclastogenesis in CIA rats. It has already been reported that methotrexate and dexamethasone can inhibit joint destruction in rats with arthritis,[36-38] but there have been no studies showing that NSAIDs including COX-2 inhibitors could prevent juxta-articular osteopenia. It may be necessary to suppress disease activity more strongly to prevent

juxta-articular osteopenia in RA patients. The present results also imply that the usual dose of celecoxib may be too low to prevent juxta-articular osteopenia in RA patients, although it is effective against inflammation. Because high-dose celecoxib could reduce juxta-articular osteopenia in CIA rats, high-dose therapy may be a possible new modality to prevent juxta-articular osteopenia in patients with RA.

In the present study, we demonstrated that indomethacin and high-dose celecoxib almost completely prevented early growth plate closure in CIA rats, while dexamethasone partially prevented growth plate destruction. We previously reported[20] that early closure of epiphyseal growth plates led to poor development of the long bones in CIA rats and showed that overexpression of matrix metalloproteinase-3 (MMP-3), which may be involved in proteoglycan degradation, and vascular endothelial growth factor (VEGF), which is associated with cartilage ossification and angiogenesis, might play a role. Therefore, VEGF may be involved in causing an increase of osteoclasts/chondroclasts, which results in destruction of the growth plate. Our histomorphometric analysis demonstrated a decrease of osteoclasts in the dexamethasone group and the cele.50 group, findings that may explain one of the mechanisms preventing growth plate destruction. Abdelrahim and Safe[39] reported that COX-2 inhibitors decrease VEGF expression by colon cancer cells, while Sanchez et al.[40] reported that NSAIDs (including COX-2 inhibitors) did not alter MMP-3 production by cultured human chondrocytes. These finding may also help to explain the mechanism by which celecoxib prevented growth plate destruction in CIA rats. On the other hand, although dexamethasone completely abolished paw swelling and juxta-articular osteopenia, it only had a limited preventive effect on growth plate destruction. It was recently reported that dexamethasone can damage the growth plate in rats by causing apoptosis of growth plate chondrocytes.[41] Therefore, the dose of dexamethasone that suppresses arthritis may concurrently have an adverse influence on the growth plate in rats. A decrease of BMD is common in children and adolescents with JIA, resulting in reduced bone mass and a higher risk of osteoporosis.[42] Taking this point into consideration, it is not only important to reduce inflammation but also bone loss in patients with JIA. High-dose celecoxib may be a new candidate to prevent juxta-articular osteopenia in patients with JIA as well as RA, while also maintaining growth plate integrity in JIA patients whose growth plates are still open.

In conclusion, our findings suggested that a selective COX-2 inhibitor, celecoxib, is not only effective against inflammation, but also prevents juxta-articular osteopenia adjacent to inflamed joints in rats with CIA. Moreover, this drug prevents destruction of the growth plates adjacent to inflamed joints, which occurs in JIA and leads to premature growth plate closure with resultant epiphyseal deformity.

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The mode of destruction in shoulders with rheumatoid arthritis based on radiographic findings

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The objective of the present study was to elucidate the mode of rheumatoid arthritis shoulder destruction. The study included 402 shoulders from 201 patients with rheumatoid arthritis. Plain radiographic findings were used to assess and statistically analyze the severity of the glenohumeral joint destruction (GHD) and greater tuberosity destruction (GTD).For both GHD and GTD scores, a statistically significant correlation was found between the left and right sides and also between the GHD and GTD scores within the same shoulder. However, 97 shoulders of 67 patients showed a heterogeneous pattern. An interesting finding was that no patients showed a combination of the GHD type plus the GTD type. Shoulders with rheumatoid arthritis showed statistically significant symmetry and uniform destruction. Even if they showed heterogeneous destruction, there were no cases of a different pattern of heterogeneity on the opposite side. The mode of destruction was not always definite, however. (J Shoulder Elbow Surg 2007;16:539-543.)

Joint destruction due to rheumatoid arthritis (RA) is well documented, and the shoulder is one of the joints most often affected.[3,11,12,13,18,19] Joint destruction caused by RA is generally bilateral and symmetrical[13,19,8,4,21]; however, we have demonstrated that joint destruction is unilateral in some patients, with a marked left versus right difference in the severity of destruction. In addition, the homogeneity of destruction within the same joint can vary.

We focused on 2 important areas of the proximal humerus, the joint surface and the greater tuberosity, because destruction of these areas seemed to be related to clinical symptoms such as joint congruity or rotator cuff function. We also wanted to determine the frequency and tendency toward heterogeneous or asymmetric destruction of the RA shoulder. We, therefore, initiated a large-scale radiographic study with the objective of elucidating the mode of RA shoulder joint bone destruction.

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MATERIALS AND METHODS

Patients

Between 2001 and 2003, 233 patients visited the Department of Orthopaedics at the Osaka University Hospital. They satisfied the diagnostic criteria established by the American College of Rheumatology[1] and underwent bilateral plain radiography. Of these 233 patients, 32 were excluded: 5 patients who had undergone joint replacement in both shoulders, 7 who had undergone joint replacement in 1 shoulder, and 20 for whom definitive radiographic findings could not be obtained for 1 or both sides. Consequently, 402 shoulders from 201 patients (26 men, 175 women) were included in this study. Their average age was 57.0 years (range, 23-84 years).

Plain radiography

Joint destruction was assessed from anteroposterior radiographs of the left and right shoulder joints taken at the final examination. The radiographs were taken by placing each patient in the supine position, tilting the contralateral side 20° relative to the direction of the x-ray tube, positioning the upper arm into lateral rotation with the palm facing upward, and then taking radiographs perpendicular to the glenohumeral joint.

Assessment of plain radiographs

Larsen's classification system[10] was used to classify glenohumeral joint destruction (GHD) into 6 grades (grades 0-5). The severity of greater tuberosity destruction (GTD) (bone erosion and radiolucency) was assessed by the depth from the top of the greater tuberosity to the bottom of the osseous lesion and was classified into 3 grades: as mild (depth, <5 mm), moderate (:depth, 5-10 mm); and severe (depth, ≥10 mm; see Figure 1).

Pattern of destruction

We classified the pattern of destruction within a shoulder into 4 types at the point of the most severely affected area as follows:

1. GHD type (heterogeneous osseous lesion in a severely eroded glenohumeral joint): GHD grade 4 or

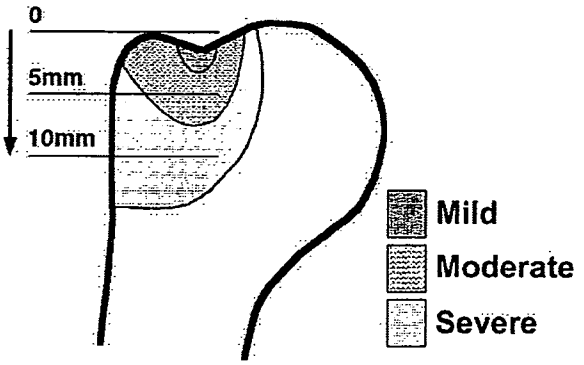

Figure 1 The destruction of the greater tuberosity was assessed by its depth from the top of the greater tuberosity to the bottom of the osseous lesion. The depth was classified into three grades: mild *(dark gray)* was less than 5 mm; moderate *(medium gray)* was between 5 and 10 mm; and severe *(light gray)* was 10 mm or more.

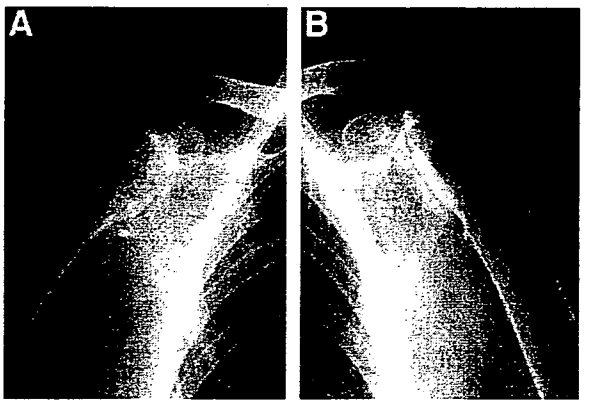

Figure 2 A and B, Radiographs of the rheumatoid shoulders of a 61-year-old woman show bilateral grade 5 glenohumeral joint destruction (GHD), and a mild grade of greater tuberosity destruction. Both shoulders showed extensive erosive destruction of articular surface, both osseous lesions of the greater tuberosity were mild. The destruction pattern was symmetric GHD type. The destruction was symmetrical.

more, GTD grade mild or moderate (see Figures 2A and B, 3A)
2. GTD type (heterogeneous osseous lesion in a severely eroded greater tuberosity): GHD grade 3 or less, GTD grade severe (Figure 4B)
3. Uniformly mild: GHD grade 3 or less, GTD grade mild or moderate (Figures 3B and 4A)
4. Uniformly severe: GHD grade 4 or more, GTD grade severe

We classified the GHD and GTD types as heterogeneous destruction.

Data analysis

Paired comparisons between men and women were performed with the Mann-Whitney *U* test for GTD and GHD scores. The correlation between age and osseous destruction, between individual left and right sides, and between the GHD and GTD scores within the same shoulder were made with Spearman rank correlation coefficients.

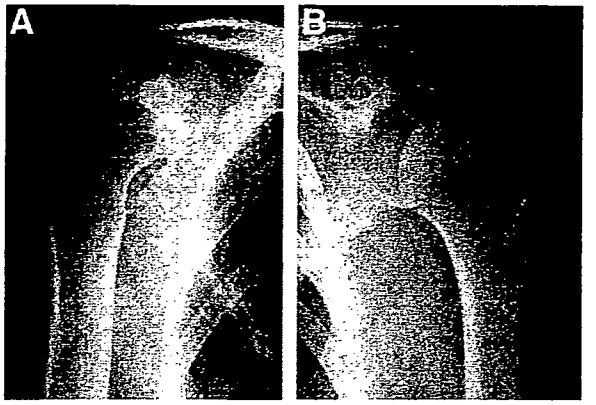

Figure 3 Radiographs of the rheumatoid shoulders of a 62-year-old woman. **A,** The right shoulder was at grade 5, and had mild GTD. It showed extensive osseous lesion in the articular surface, but there was little osseous lesion in the greater tuberosity. The destruction pattern was GHD, uniformly mild type. The destruction was asymmetrical. **B,** The left shoulder showed no pronounced lesion and was at glenohumeral joint destruction (GHD) grade 1. It had a mild grade of greater tuberosity destruction (GTD).

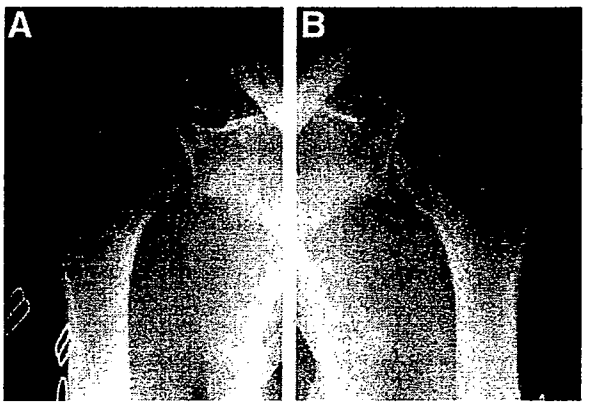

Figure 4 Radiographs of the rheumatoid shoulders of a 52-year-old woman. **A,** The right shoulder was at glenohumeral joint destruction (GHD) grade 1 and had a mild grade of greater tuberosity destruction (GTD). It showed no pronounced osseous lesion. **B,** The left shoulder was at GHD grade 2 and a severe grade of GTD. It showed an extensive osseous lesion in the greater tuberosity, but the original articular surface had not yet disappeared. The destruction pattern was uniformly mild/GTD type. The destruction was asymmetrical.

RESULTS

Classification of glenohumeral destruction and greater tuberosity destruction

Glenohumeral destruction. According to a. Larsen's classification system, the severity of GHD was classified

Table I Radiographic assessment by Larsen method of the glenohumeral joints in 201 patients with rheumatoid arthritis*

	Right GHD grade						
	0	1	2	3	4	5	Total
Left GHD grade (No. of joints)							
0	2	0	0	0	0	0	2
1	0	30	17	0	1	3	51
2	0	10	47	12	1	3	73
3	0	0	9	9	4	1	23
4	0	0	3	1	5	4	13
5	0	3	2	1	5	28	39
Total	2	43	78	23	16	39	201

GHD, Glenohumeral joint destruction.
*The number of the left GHD grade for each right GHD grade is presented. The grade of GHD between individual left and right sides is significantly correlated ($r = 0.69$, $P < .001$).

Table II Radiographic assessment of the greater tuberosity destruction in 201 patients with rheumatoid arthritis*

	Right GTD grade			
	Mild	Moderate	Severe	Total
Left GTD grade (No. of joints)				
Mild	48	17	4	69
Moderate	9	75	14	98
Severe	2	8	24	34
Total	59	100	42	201

GTD, Greater tuberosity destruction.
*The number of the left GTD grade for each right GTD grade is presented. The grade of the GTD between individual left and right sides is significantly correlated ($r = 0.65$, $P < .001$).

into 6 grades: grade 0 in 4 joints (1.0%), grade 1 in 94 joints (23.3%), grade 2 in 151 joints (37.6%), grade 3 in 46 joints (11.4%), grade 4 in 29 joints (7.2%), and grade 5 in 78 joints (19.4%). Thus, 107 (26.7%) of 402 joints had a grade of 4 or more (Table I).

Greater tuberosity destruction. As described earlier, the severity of the GTD was classified into 3 grades: mild in 128 shoulders (31.8%), moderate in 198 shoulders (49.3%), and severe in 76 shoulders (18.9%; Table II).

Statistical analysis

A comparison of gender and GHD or GTD scores found no significant difference between men and women in GHD ($P = .26$) and GTD scores ($P = .67$).

There was no correlation between age and the GHD ($r = 0.11$; $P = .03$) or GTD ($r = -0.09$; $P = .35$) scores. Significant correlations were found between the individual left and right sides (Tables I and II) for both. GHD ($r = 0.69$, $P < .001$) and; GTD ($r = 0.65$, $P < .001$) and between GHD and GTD ($r = 0.58$, $P < .001$) within the same shoulder (Table III).

Table III The number of the greater tuberosity destruction grade is presented for each glenohumeral joint destruction grade in 402 shoulders from 201 patients*

	GHD grade						
	0	1	2	3	4	5	Total
GTD grade (No. of joints)							
Mild	4	63	54	6	0	1	128
Moderate	0	31	82	22	16	47	198
Severe	0	0	15	18	13	30	76
Total	4	94	151	46	29	78	402

GTD, Greater tuberosity destruction; *GHD,* glenohumeral joint destruction.
*There was a significant correlation between the grade of GHD and GTD ($r = 0.58$, $P < .001$).

Table IV The pattern of the opposite side is presented in 67 patients with heterogeneity of destruction

	Pattern of opposite side			
	Uniformly mild*	Symmetric	Uniformly severe†	Total
GHD type	13	22	7	42
GTD type	14	8	3	25
Total	27	30	10	67

GHD, Glenohumeral joint destruction; GTD, greater tuberosity destruction.
*GHD grade ≤3, GTD grade is severe.
†GHD grade ≥4, GTD grade mild or moderate. No case showed asymmetric heterogeneous pattern.

Heterogeneous destruction within a shoulder

We showed that there was a significant correlation between the GHD and GTD scores within the same shoulder. However, we investigated 97 shoulders (24.1%) from 67 patients who showed a heterogeneous pattern within their shoulders of the GHD type (64 shoulders in 42 patients) and GTD type (33 shoulders in 25 patients).

We then assessed the pattern of destruction on the opposite side for these patients (see Table IV). In the GHD type, 22 (52.4%) of 42 patients showed a symmetrical pattern. In the same manner, in the GTD type, 8 (32.0%) of 25 patients showed a symmetrical pattern. No patients presented with heterogeneous patterns in which there was a combination of the GHD type and the GTD type.

DISCUSSION

In general, joint destruction caused by RA is bilateral and symmetrical.[4,8,13,19,21] One study showed that the left-right symmetry of the severity of joint destruction was especially pronounced in patients with severe RA.[13] Similarly, in the present study, there was a statistically significant correlation in the GHD and GTD scores between the left and right sides. In addition, a significant correlation was found between the GHD and GTD scores within the same shoulder.

Many studies[4,8,13,19,21] have compared the presence of joint destruction between left and right shoulders but did not compare the severity of destruction between the sides or between different areas within the same shoulder. Like previous reports on shoulder joint destruction, the present study involved many patients. Many patients were mildly affected, however, and that may have reduced the probability that we could detect statistically significant differences between individual sides or the mode of destruction within a joint.

We believe that the joint surface and the greater tuberosity are clinically important parts of the proximal humerus because of their role in joint congruity and rotator cuff function, respectively. Lehtinen et al[13] confirmed radiographically that the mildest sign in the rheumatoid shoulder is marginal erosion on the superolateral articular margin of the humerus. We therefore assessed the presence of osseous lesions of these 2 areas.

The present study assessed,the severity of GHD and GTD. There were correlations in the GHD and GTD scores between the same sides (Tables I and II) and between the GHD and GTD scores within the same shoulder (Table III). With respect to GHD, only 18 patients (9.0%) showed a clear difference between their left and right sides (>2 grades separation; Table I). With respect to GTD, only 6 patients (3.0%) showed a clear difference between their left and right sides (>2 grades separation; Table II). Conversely, within the same shoulder, 97 shoulders from 67 patients that showed a heterogeneous pattern: 64 shoulders from 42 patients for the GHD type, and 33 shoulders from 25 patients for the GTD type. In the GHD type, 22 (52.4%) of 42 patients showed a symmetrical pattern. Similarly, in the GTD type, 8 (32.0%) of 25 patients showed a symmetrical pattern. An interesting finding was that no patients showed a combination of the GHD type plus the GTD type (Table IV).

This suggests that most patients showed uniform and symmetrical destruction. Even if the cases showed heterogeneous destruction within the same shoulder, the opposite side always showed a symmetrical, heterogeneous pattern or uniform destruction. This did not seem to be a random occurrence.

We considered 2 factors that might cause this variety of destruction. First, absorption of the cartilage and bone as a result of the actions of cytokines released from the synovial tissue or direct destruction of the marginal bone may have resulted in these differing patterns. The second factor was the effects from anatomic and mechanical factors. Some studies have shown that mechanical stress can affect shoulder destruction. Other studies have found that hand dominance has no effect on the severity of joint destruction, suggesting that mechanical stress has little effect.[11-14] Because the shoulder joint is not a weight-bearing joint, mechanical stress may have a lesser effect than for weight-bearing joints such as the hip or knee. However, we could not generate a reliable hypothesis in this study to explain our results adequately. Ochi et al[18] reported that even in the same joint, the mechanism of destruction varies widely depending on the disease subset.

The condition of the bone and cartilage may affect the progression of bony destruction. This may be further affected by several factors, such as age, gender, medication, and the duration of the disease.[2,5-8,15,18,20] In this study, the severity of both GTD and GHD types did not seem to be affected significantly by gender or age in the statistical analysis. All of the present patients received some form of medication, but the drugs used and the time course of administration varied widely, making it difficult to assess the effects of drug-induced bone destruction. Furthermore, the disease durations were not assessed because of a lack of information from the patients. Regrettably, we could not assess other factors, such as laboratory data or the condition of the rotator cuff, joint cartilage, or bone marrow. Further studies are required to determine the mechanism of joint destruction using magnetic resonance imaging or more detailed clinical data.

In conclusion, shoulders with RA showed statistically significant symmetry and uniform destruction on plain radiographs. Even if the shoulders showed heterogeneous destruction, no patients presented with a different pattern of heterogeneity on the opposite side. The mode of destruction was not always definite, however: some subjects showed heterogeneous destruction within a joint, and a few showed unilateral destruction or a difference in the degree of destruction between left and right sides.[9,16,17]

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In Vivo Three-Dimensional Skeletal Alignment Analysis of the Hindfoot Valgus Deformity in Patients with Rheumatoid Arthritis

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ABSTRACT: The purpose of this study was to analyze the skeletal alignment of the hindfoot valgus deformity in patients with rheumatoid arthritis using bone models reconstructed from three-dimensional computerized tomography data. Computed tomography was performed on 21 feet of patients with rheumatoid arthritis, and magnetic resonance imaging was taken of 10 normal feet of eight volunteers. An image processing system was used to create bone models and analyze the three-dimensional displacement of the calcaneus, talus, navicular, and cuboid bones. With a standard coordinate system in the distal tibia and a local coordinate system in each bone of the hindfoot, three rotational parameters and three translational parameters were used to evaluate the relative displacement. The talus showed plantar flexion. Both the calcaneus and navicular bones had valgus and lateral shift displacements. However, the cuboid had no displacement relative to the calcaneus, and the navicular showed no displacement relative to the cuboid. The calcaneus, navicular, and cuboid bones have the same pattern of deformity in patients with rheumatoid arthritis. This three-dimensional image-based technique successfully quantified the hindfoot valgus deformity resulting from rheumatoid arthritis and is beneficial for better understanding the deformity pathomechanism. © 2006 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 25:330–339, 2007

Keywords: three-dimensional; skeletal alignment; hindfoot valgus deformity; rheumatoid arthritis

INTRODUCTION

Pes planovalgus deformity is a predominant hindfoot deformity in patients with rheumatoid arthritis (RA) with a prevalence of 46% to 64%.[1–5] Vahvanen reported that 87.4% of 292 surgically treated patients with RA showed pes planovalgus.[6] The clinical description of pes planovalgus deformity includes heel valgus, arch height loss, and forefoot abduction.[3–7] Although forefoot deformities are often the presenting complaints, as disease progresses, hindfoot involvement is a dominant, disabling defect that may need surgical stabilization and correction.[4,7,8]

Many clinicians and researchers have analyzed the deformity pattern using various methods, because analysis of the skeletal alignment of hindfoot valgus deformity in RA patients is crucial for understanding pathogenesis and the mechanism of the deformity and for preoperative planning. However, plain radiography lacks precision and accuracy, and images are difficult to obtain and measure in some RA patients.[7,9,10] Selzer and colleagues used two-dimensional (2D) coronal computed tomography (CT) to assess hindfoot valgus deformity.[8,11] This method did not allow a complete evaluation in three-dimensional (3D) ways and failed to reflect the deformities of the cuboid and navicular bones. Woodburn and colleagues used 3D imaging techniques to analyze the geometric architecture of the subtalar and midtarsal joints in cases of RA based on magnetic resonance imaging (MRI).[5] The twenty-four parameters they used are relatively complicated and can not provide clinicians with a good visualization of the deformity pattern.

In vivo 3D bony structural analysis of hindfoot valgus deformity in RA patients remains largely unexplored. A 3D imaging-based technique was developed by Osaka University to analyze bone

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