ハンス島の細胞からのインスリン分泌の不全で起きるが，これには様々な遺伝子，蛋白，小分子が関係する可能性があり，蛋白はmRNAから合成され，mRNAはゲノム配列であるDNAの情報をもとに合成される．

したがって医療や健康維持の最終的な目的は個体レベルであるが，それは結局ゲノム情報により読み取れる可能性がある．ゲノム情報が個体の健康や疾患に直接結び付いている例は単一遺伝子病(メンデル型疾患)である．単一遺伝子病では約30億のゲノム配列のどこかに変異があり，そのため特定の遺伝病になる．ゲノム変異と個体の健康状態の対応が一対一であり，極めて理解しやすい．しかし，多くの場合，それは期待できない．多くの頻度の高い疾患(common disease)の原因は単一遺伝子ではない．これらは多因子疾患とよばれ，多くの遺伝子と環境要因が関係していると考えられている．

先制医療の目的は未来の健康障害を予測して，その出現を予防することである．ゲノムを先制医療に用いる場合，単一遺伝子疾患では単純な論理が存在する．ゲノム上の変異で疾患の発症が予測できるので，発症の予防法を考えればよい．たとえばフェニルケトン尿症などではすでに予防的治療が実行されている[4]．

以上の議論はすべて生殖細胞系列のゲノム情報についてのものである．それ以外にも，癌ゲノム情報も重要である．以前より癌ゲノムについては癌遺伝子，癌抑制遺伝子などが発見され，薬物治療や予後予測に有用である場合があることがわかっていた．しかし，最近では全ゲノム情報から変異を発見することが可能になっている[1]．

遺伝病，多因子疾患に対する先制医療に生殖細胞系列ゲノム情報が有効であろうか．また種々の癌に対して癌ゲノム情報が有効であろうか．本項では種々の面からの検討を行う．

2 ゲノム疫学研究の現状

a. 連鎖解析

ヒト全ゲノム配列が発表された2003年以前にもゲノム上のマーカー探しがさかんに行われた．特に有効に使われたマーカーがマイクロサテライト(short tandem repeat polymorphism：STRP)である．マイクロサテライトの多くは2～4塩基の繰り返し配列の繰り返し回数の違いによる多型である．比較的変異速度が速く，しばしば多アリルの多様性が存在するためマーカーとして適している．全ゲノム上にマーカーを300～500個程度配置すれば1マーカーについて平均10^7ヌクレオチド領域をカバーできることになり，全ゲノム領域を対象とした連鎖解析に用いることができる(最近では1万個以上の一塩基多型〈single nucleotide polymorphism：SNP〉を用いることもある)．

連鎖解析(特にパラメトリック連鎖解析)[注]は単一遺伝子疾患の原因座位を検索するために極めて有効な手段である[5]．マーカー座位と疾患原因座位の連鎖を利用して後者の染色体上の位置を検索する．パラメトリック連鎖解析を行うためにはメンデル型遺伝に従う家系情報が必要である．多くの家系構成員の各個人について表現型情報とゲノム上に置かれた約300～500のマイクロサテライトマーカーについての遺伝型データがあれば，連鎖解析により疾患関連座位と連鎖する(染色体上で近傍にある)マーカーを検索することが可能である[5]．パラメトリック連鎖解析では最尤法に基づいたロッド値(lod score)を求め，ロッド値が3を超えれば連鎖が存在する可能性が強い[5]．疾患関連座位と連鎖するマーカーがわかれば，染色体の地図情報から原因遺伝子をさがす．連鎖解析の理論自体は尤度，最尤法，EMアルゴリズム，隠れマルコフ過程などを用いるため極めて難解であるが，Linkage package，Genehunter，MARLINなどの

注 パラメトリック解析は，遺伝形式を仮定して染色体上の原因遺伝子を絞り込んでいく遺伝統計学的手法である．尤度(もっともらしさ)を用いた最尤法で解析する．なお一切の前提なしに解析するのが，ノンパラメトリック解析である．

コンピュータプログラムが提供されており，誰でも用いることができる[5]．

たとえば，慢性腎不全と高尿酸血症をきたす，家族性若年性高尿酸血症性腎症（familial juvenile hyperuricemic nephropathy）では連鎖解析により16p12に存在するマーカーとの連鎖が報告され[6]，その後，その場所にUMOD（uromodulin）遺伝子が原因遺伝子として見出されている[7]．

パラメトリック連鎖解析により多くの遺伝病の原因遺伝子が明らかになった後，ゲノム研究者の興味は多因子病に向かった．たとえば，糖尿病，関節リウマチなどの疾患に関与する遺伝子の発見である．まず登場したのがノンパラメトリック連鎖解析である[5]．特に，その中で罹患同胞対解析がさかんに行われた．同胞ともに同じ疾患にかかった家系を多く集め，同胞が共有しているゲノム上の座位を検索する方法である．しかし，残念ながらノンパラメトリック連鎖解析はそれほど成功しなかった．原因は検出力がそれほど高くなかったことと，連鎖する領域が見つかってもメンデル型遺伝病とは異なって，その領域で関連遺伝子を検索することが容易ではなかったことにある[5]．

ゲノムワイド関連解析（GWAS）

ノンパラメトリック連鎖解析に次いで登場したのがゲノムワイド関連解析（genome-wide association study：GWAS）である．これはゲノム上の各座位について特定の形質（たとえば糖尿病の有無）と関連があるかどうかを調べる方法である．関連がある座位は必ずしも直接形質と関連がある必要はない．その理由は，ヒトゲノム上には連鎖不平衡という構造が存在するからである．

連鎖不平衡とは，染色体上の近傍にある二つの座位のアリルの関連である[5]．たとえば，第一座位（A/C），第二座位（T/A）に関して，第一座位がAであると第二座位は独立な場合よりもTである可能性が高いとき，連鎖不平衡があるという．もし第一座位が疾患に関連する座位であり，第一座位と第二座位の間に連鎖不平衡があれば，第二座位も疾患と関連する．これが連鎖不平衡を利用した関連解析の原理である[5]．

しかし，連鎖解析と連鎖不平衡の違いは，連鎖が10^7ヌクレオチドの領域にも及ぶのに比較して，連鎖不平衡は10^4ヌクレオチド程度であるということである．また連鎖と異なって，連鎖不平衡の及ぶ範囲は染色体の場所によって大きく異なる．したがって，全ゲノム領域をカバーするために必要なマーカー数が10^3倍も違う．そのため，連鎖解析は300～500のマーカーで行うことができたが，連鎖不平衡を利用した関連解析では30～50万個以上のマーカーが必要となるのである．これだけの数のマーカーを整備するために時間がかかりGWASの開始が遅れた．

連鎖解析で用いられたマーカーはマイクロサテライトマーカーであったが，連鎖不平衡を用いた関連解析に用いられたマーカーは一塩基多型である．ヒト集団では極めて多数のSNPが存在し，最初は10万個程度のSNPを用いたゲノムワイド関連解析が行われた[8]．その後，HapMapプロジェクトが行われ[9]，連鎖不平衡ブロックの情報を用いたマーカー選択が行われた．連鎖不平衡ブロックとは，その中で比較的強い連鎖不平衡の存在するゲノム上の領域であり，数kb～数10kbの長さのことが多い．その結果，数十万個のSNPを用いたGWASが行われるようになった[10]．

世界で最初にGWASを行ったのは理化学研究所の中村のグループである[8]．最初の論文は2002年に心筋梗塞に対して行われたGWASであるが，その後，関節リウマチを対象としたGWASが行われた[11,12]．わが国以外で最初にGWASを発表したのはKlein[13]である（2005年）．そして2007年にWellcome Trustによる膨大なデータをもとにしたGWASデータが発表され[10]，世界的にGWASが広がった．その後，GWASを行うためのチップはコマーシャルに広く販売されるようになって現在に至っている．

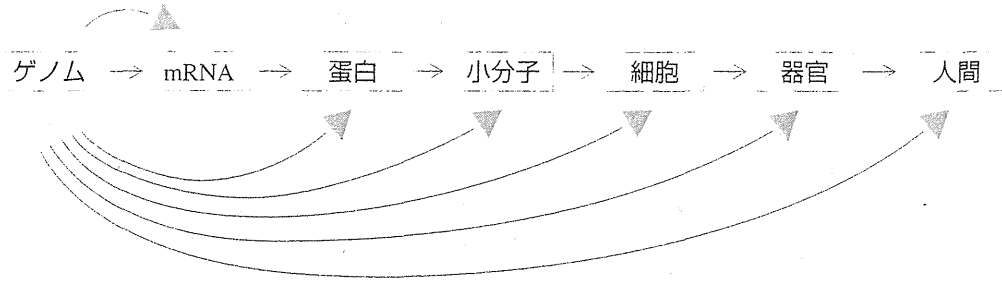

図1 ゲノムワイド関連解析(GWAS)研究の概要
GWASは基本的にゲノムの多様性と形質の多様性の関連を調べる研究である.

GWASは基本的にゲノムの多様性と形質の多様性の関連を調べる研究である. 形質は様々なレベルで存在しうる. mRNA, 蛋白, 小分子, 細胞, 臓器, 個人(図1)など各レベルで形質は存在する. たとえばmRNAの発現量, 蛋白, 小分子の量, 細胞の数や大きさなどは形質である. しかし, 最も典型的な形質は個人レベルの形質であり, たとえば身長, 体重, 疾患の有無, 薬物反応性などである.

初期のGWASは疾患の有無について行われた. しかし, 次第に薬物反応性を対象としても行われるようになり[14,15], さらに分子や細胞を対象に行われるようになった[16]. また, 生理学的検査値もGWASの対象となりうる. たとえば, 心電図のQT間隔[17], 肺活量[18]などである.

生化学的臨床検査値, 血液検査値もGWASの対象となり, たとえば血清尿酸値に関連する遺伝子などが詳細に解析されており[16,19], 多数のトランスポーター遺伝子が関連することがわかっている.

c シークエンサーを用いた解析

GWASによる解析により多数の遺伝子と形質の関連が発見された. しかし, たとえばGWASでは単一遺伝子疾患に関連する遺伝子などはほとんど発見できない. その理由は, GWASで対象となるSNPは比較的頻度の高いSNPが多く, 頻度の低いSNPは含まれていないからである. 頻度の低いSNPは比較的新しい変異による可能性が高く, それぞれの家系に特有の変異であることもしばしばある. そのように低い頻度の変異と形質との関連はGWASで発見することは困難である.

また, GWASで発見された関連遺伝子による形質への効果は比較的小さく, 発見されたすべてのSNPの効果を集めても, 双子研究などから得られた遺伝力(heritability)を説明するほどの大きな効果にはならないことが知られている. このギャップ(missing heritability)を説明する要因として, 頻度が低く, 効果の強い変異の存在が指摘されている. それらの変異は低頻度のためGWASでは発見されず, 残っている可能性がある[20].

原因遺伝子の候補が比較的絞られている場合はサンガー法を用いたシークエンサー(塩基配列の分析装置)は十分な機能を発揮した. ヒトゲノム配列の決定や, HapMapプロジェクトで用いられたシークエンサーには速さの点で限界があった. しかし, 最近導入されたいわゆる次世代シークエンサーはこれまでとは全く異なった原理を用いたものであり, 膨大なゲノムデータを短時間で処理することができるようになった. たとえば1週間で10^9～10^{10}ヌクレオチド程度のシークエンスが行えるようになってきた. そうなると, SNPチップではなく, シークエンサーを用いてゲノムと遺伝子の関連が解析できるようになる.

まず, 個人の全ゲノム配列が決定できるようになった. 2007年にはサンガー法によりVentorの個人ゲノムが公表されたが[21], 2008年に発表されたWatsonのゲノム配列は次世代シークエンサーを用いて行われた[22]. 日本人の全ゲノ

ム配列も2010年に理化学研究所より発表された[23]．

エクソンの部分は全ゲノム配列の2%程度である．したがって，6×10^7ヌクレオチド程度と考えられる．エクソンの領域のみを選択的に抽出する方法が開発された(エクソンキャプチャー法)．これを用いて全ゲノムのエクソン配列の変異を検出すれば多くの遺伝病の原因変異を発見できる可能性がある．前述のように，パラメトリック連鎖解析はメンデル型遺伝病に関連する変異の発見のための強力な手段である．しかし，連鎖解析で陽性となる領域は非常に広く10^7ヌクレオチド程度である．この領域のエクソン配列を読むことにより効率的に遺伝病に関連する変異を発見できる[24]．

また，致死的な遺伝病では家系情報が得られないこともしばしばある．そのような場合はパラメトリック連鎖解析は不可能であり，最初から直接エクソンの配列を読むことにより原因変異を発見できる[25]．

しかし，問題の1つは次世代シークエンサーによる配列は必ずしも100%正しくはないことである．たとえエラーの頻度が10^{-5}であったとしても，6×10^7ヌクレオチドには600個の誤った一塩基多様性(SNV：single nucleotide variation)が存在することになる．したがって，次世代シークエンサーで発見された変異をサンガー法で確認する必要があることが多い．さらに，サンガー法で真の変異と確認できても，多くの場合，数個以上の変異が原因変異の可能性として残る．そして，個々の変異が本当に遺伝病の原因変異であるかの証明が必要になることが多い．その場合，変異の効果を統計学的に予測することに加え，家系情報が極めて強力であることもしばしばである．同じ家系の遺伝病では，ほとんどの場合，疾患の有無はゲノム上の変異を基礎にしたメンデルの法則で決まることがわかっているからである．

多因子疾患のゲノム解析にもシークエンサーを用いる試みがはじまっている．しかし，正確性や価格の点で，SNPチップの補助がまだ必須である．

次世代シークエンサーは癌ゲノムの配列決定にも用いられている．国際癌ゲノムコンソーシアムが開始され，わが国ではウイルス性肝癌を担当することになっている．最近，27の肝癌ゲノムの変異のプロフィールが発表された[1]．それによると癌細胞には生殖細胞系列のゲノム配列に比較して極めて多い変異が存在する(数千～数万個)．複数の癌患者の癌ゲノムに共通する変異も存在する．そのようなデータを積み重ねながら，どの変異が癌に特有なのか，治療や予後に関係するのかが今後の研究の対象となる．

今後，シークエンサーはさらに高速に，安価になる．ボトルネックは情報解析，コンピュータ性能と配列の正確性である．また，発見された変異の意味付けが最終的な重要事項になるであろう．

3　ゲノム情報の臨床，予防への応用

ゲノム情報利用のために考慮する要素

個人のゲノム情報(癌のゲノム，候補遺伝子のゲノムの情報を含む)を医療や予防，さらには健康維持に用いるために考慮する要素は4つにまとめられている．

まず分析的妥当性は，常に同じ結果を戻す信頼できる検査システムにより保証される．今後，日本臨床検査標準協議会(JCCLS)などによる活動の一般化が期待される．

特定の形質(疾患や薬物反応性)に特定のゲノムマーカーを使用するためには，まず2つの間の関連が確実に示されなければならない．単一遺伝子病の場合を除き，多くの場合，臨床的妥当性は疫学的研究から得られる．疫学的研究の中でも症例・対照研究から得られる場合が多い．まず関連の確実性は統計学的な結果の判定(検定)に用いられる閾値であるP値により示される．しかし，この場合，検定を複数回行うことにより，その中で低いP値が生じやすい

という問題を十分考慮する必要がある．たとえば，前述のゲノムワイド関連解析で多くのゲノムマーカーを使用する場合，5×10^{-8}という極めて低いP値が必要であり，しかも独立した標本による再現研究が必要である．

しかし，関連の確実性を示すP値だけでは十分ではない．関連の強さを示す効果サイズの推定，さらにはゲノムマーカーを使用した場合の表現型発現確率の変化の大きさを推定する必要がある．症例・対照研究で得られる効果サイズはオッズ比(OR)で示され，有病率が低い場合はオッズ比と相対リスクは近いことが知られている．さらに，症例群の中での検査陽性の割合(感度)，対照群の中での検査陰性の割合(特異度)をできる限り正しく推定する必要がある．さらに，集団の中の検査陽性の人々が疾患をもつ確率(陽性的中率〈positive predictive value：PPV〉)，集団の中の検査陰性の人々が疾患をもたない確率(陰性的中率〈negative predictive value：NPV〉)を推定することが望ましい．感度や特異度は症例・対照研究で推定できるがPPV，NPVは全集団調査(コホートなど)により推定できる．症例・対照研究からPPV，NPVを推定するためには有病率を仮定する必要がある．

研究者が陥りやすい誤りは，感度と特異度が高いことにより臨床応用の妥当性を判断することである．有病率が極めて低いときには感度と特異度が高くてもPPVは低いことがしばしばある．すなわち，検査を臨床応用し，陽性と判定された個人が疾患や薬物反応性を発現する確率がPPVなので，この値が高くないと臨床応用の妥当性は保証できない．また，陰性と判定された個人が表現型を発現しない確率(NPV)も高くなければならない．これらの値は先制医療を考え出るうえで極めて重要な要素である．

臨床的有用性を考えるうえで，感度，特異度，PPV，NPVの推定値は重要である．しかし，それに加え表現型の重症度，予防法や治療法の有無，医療経済的な問題なども考慮の対象である．たとえば，ある薬物の副作用に関連するゲノムマーカーが見つかったとする．そのゲノムマーカーの有用性は副作用の重症度にも関係する．さらに，ゲノムマーカーの検査費用も関係があるであろう．疾患の発症を予測するゲノムマーカーであれば，予防法や治療法の有無も有用性に関係する．これらを考慮して臨床的有用性が示された場合，実際にそれを臨床や予防的に用いることを考慮してもよい．

倫理的，法的，社会的問題(ELSI：ethical, legal and social issue)も十分考慮する必要がある．ELSIの重要性は生殖細胞系列遺伝情報の場合特に大きいが，体細胞遺伝情報や発現情報の場合は小さい．

ゲノムマーカーの臨床や予防への応用

ゲノムマーカーは様々な分野で臨床応用されている．極めて有効な分野はゲノム薬理学と癌に対するゲノムマーカーである．疾患に対するゲノムマーカーの利用は創薬のターゲットとしての応用に注目が集まっているが，疾患の予測への応用はこれからである．

ゲノム薬理学については様々なゲノムマーカーと薬物の効果，副作用との関連が発見されている．多くのスティーブンス・ジョンソン症候群(Stevens-Johnson syndrome：SJS)，TEN(toxic epidermal necrolysis)の原因がHLAの特定のアリルであることがわかった．たとえば*HLA-B*1502*とカルバマゼピンによるSJS-TEN[26]，*HLA-B*5801*とアロプリノールによるSJS-TEN[27]などである．しかも，関連するHLAアリルは薬物により異なるだけではなく，人種によっても異なる．これはHLAアリルの頻度が人種によって大幅に異なるからである．

たとえば前述の通りカルバマゼピンとSJS/TENの関連は漢民族で発表されたが，日本人と白人ではむしろ*HLA-A*3101*が関連している[28,29]．アロプリノールと*HLA-B*5801*との関連も漢民族において強いが，日本人でも同じ関連が発表されているものの*HLA-B*5801*遺伝子の頻度は極めて低い[30]．アバカビルと*HLA-B**

5701 との関連については実際に遺伝子検査を行った群のほうが行わなかった群より副作用が少なかったことが報告されている[31]．

台湾においてはカルバマゼピン，アロプリノールをはじめて服用する前には遺伝子検査が義務づけられている．それにより SJS/TEN の頻度を減らすことができると期待されている．わが国では医薬品の添付文書にゲノム情報と副作用の関係が記載されているものはあるが（イリノテカンと *UGT1A1*，カルバマゼピンと前述の HLA，アロプリノールと前述の HLA）[32]，遺伝子検査が義務化されているものはない．ゲノム薬理学的発見は相次いでいるので今後実際の応用に用いられると思われる．

以上は生殖細胞系列のゲノム多様性によるゲノムマーカーについてのものである．最近では体細胞ゲノム変異をゲノムマーカーとして用いる臨床応用の報告が相次いでいる．たとえばゲフィチニブの感受性に関係する *EGFR* 遺伝子[33]，セツキシマブの感受性に関係する *K-Ras* 遺伝子[34]，vemurafenib の効果に関与する *BRAF* 遺伝子[35]などである．

4　先制医療の実現に向けた課題

先制医療のためにはできる限り正確な疾患の予測を行う必要がある．例をとると骨折の予防に用いられるビスフォスフォネート製剤がある．世の中に骨折のリスクがゼロの人は存在しないので，すべての人が予防的に服用すべきである，という論理は正しくない．必ず骨折を起こす人もほとんど存在しないので，だれも服用すべきではない，という論理も正しくない．得られるあらゆる情報を集めて，特定の値以上の確率で骨折を起こすと予測される人が服用すべきであろう．

そのような予測の下に開発されたソフトウェアが FRAX® であり，ポアソン回帰を使用している[36]．予測のためには年齢，性別，身長，体重，骨折歴，喫煙，アルコール，体格指数（BMD），関節リウマチの存在，ステロイド服用など多くの因子を取り入れている．そのためには多くの人々から得られた疫学データが必要である．疫学研究には膨大な費用と労力が必要であるが，それにより膨大な医療費が節約でき，本当に予防が必要な人々に予防的治療ができることを考えれば正当化できる費用と労力である．しかし，FRAX® の応用はわが国では欧米より盛んではないようである．

越智らは，インターフェロンとリバビリンによるC型肝炎治療の成功の有無を，年齢，ウイルス量，ウイルスの遺伝型，AST/ALT 比，IL28B 遺伝型（患者の遺伝型），アルファフェト蛋白の多因子を用いてロジスティック回帰モデルで予測する提案をしている[37]．

しかし，わが国の医師はこのような確率的な考えに慣れていない．アメリカの臨床の教科書には最初に尤度，オッズ比，感度，特異度，PPV，NPV などの概念が詳しく説明されている場合も多く，診断行為，治療行為が必ずしも100% 成功するわけではないことを前提に医療を行うことに慣れている．わが国では医療行為，治療行為の結果が 100% 予測できるという考えをもつ人々が多く，様々な方面に悪影響を与えている．社会やマスメディアが不可能な100% を要求するために，心ならずも完全性を装わざるを得ない面もあるであろう．

ゲノムマーカーにより 100% 予測できるのは100% の浸透率をもつ単一遺伝子病の場合である．その他の場合には複数の遺伝子と複数の環境要因が関与しており，予測は 100% ではなく確率的であることを知る必要がある．さもないと，先制医療はわが国では過剰医療をもたらす可能性さえある．

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1973(昭和48)年東京大学医学部卒．東京大学病院，アメリカスクリプス研究所，ミシガン大学客員教授，東京女子医科大学膠原病リウマチ痛風センター(センター長)，理化学研究所ゲノム医科学研究センター(センター長)を経て現職．現在は，株式会社スタージェン情報解析研究所所長，東京女子医科大学客員教授，公益財団法人痛風財団理事長．
内科学，リウマチ学，核酸代謝，統計学疫学，遺伝学，ゲノム薬理学，バイオインフォマティックスなど幅広い分野をテーマとして研究をしています．
わが国の社会や産業にも非常に興味をもっていろいろな本を読んでいます．現在の閉塞感を打ち破るには教育や産業を大改革し，健康，医療，介護などに雇用の場を広げる必要があるのではないでしょうか．

Mod Rheumatol (2012) 22:654–658
DOI 10.1007/s10165-011-0575-8

ORIGINAL ARTICLE

Magnetic resonance imaging (MRI) detection of synovitis and bone lesions of the wrists and finger joints in early-stage rheumatoid arthritis: comparison of the accuracy of plain MRI-based findings and gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI-based findings

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Received: 25 July 2011 / Accepted: 25 November 2011 / Published online: 28 December 2011

Abstract
Objective To explore whether synovitis and bone lesions in the wrists and finger joints visualized by plain magnetic resonance imaging (MRI)-based findings correspond exactly or not to those judged by gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI-based findings.

Methods Magnetic resonance imaging of the wrists and finger joints of both hands were examined in 51 early-stage rheumatoid arthritis (RA) patients whose median disease duration from the onset of articular manifestations to entry was 5 months, by both plain (T1 and short-time inversion recovery images) and Gd-DTPA-enhanced MRI (post-contrast fat-suppressed T1-weighted images) simultaneously. We focused on 15 sites per hand, to examine the presence of synovitis and bone lesions (bone edema and bone erosion). Gd-DTPA-enhanced MRI-based findings

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were considered "true" lesions, and we evaluated the accuracy of plain MRI-based findings in comparison to Gd-DTPA-enhanced MRI-based findings.

Results Synovitis, judged by plain MRI-based findings, appeared as false-positive at pretty frequency; thus, the specificity, positive predictive value and accuracy of the findings were low. The rate of enhancement (E-rate) in false-positive synovitis sites was significantly low compared with true-positive synovitis sites where Gd-DTPA enhancement appears. In contrast to synovitis, the false-positivity of bone lesions, judged by plain MRI-based findings, was very low compared with Gd-DTPA-enhanced MRI-based findings.

Conclusion Synovitis judged by plain MRI-based findings is sometimes considered false-positive especially in sites where synovitis is mild. However, plain MRI is effective in identifying bone lesions in the wrist and finger joints in early-stage RA.

Keywords Early-stage RA · Plain MRI · Gd-DTPA-enhanced MRI · Synovitis · Bone lesions

Abbreviations

ACR	American College of Rheumatology
CRP	C-reactive protein
E-rate	Rate of enhancement
Gd-DTPA	Gadolinium–diethylenetriamine pentaacetic acid
HLA-DRB1*SE	HLA-DRB1*shared epitope
RA	Rheumatoid arthritis
UA	Undifferentiated arthritis

Introduction

Magnetic resonance imaging (MRI) reveals joint inflammation and damage in early-stage rheumatoid arthritis (RA) [1–4] that take the form of synovitis and bone lesions, including bone edema and bone erosion [1–4]. As active synovial lesions in patients with RA are rich in vascularity, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI-based findings have become the gold standard to evaluate joint inflammation and damage in RA [1]. Accordingly, by assessing Gd-DTPA-enhanced MRI-based findings of the wrists and finger joints of both hands, we have determined that symmetrical synovitis and bone lesions are important predictors of the development of RA in patients with undifferentiated arthritis (UA) [5–8]. In these earlier studies, we did not specifically compare Gd-DTPA-enhanced MRI-based findings with plain MRI-based findings. However, Gd-DTPA-enhanced MRI is an expensive diagnostic tool compared to plain MRI, and Gd-DTPA can induce serious adverse events [9]. Thus, if plain MRI is sufficiently sensitive for the purpose, it should be possible to reduce both the cost and the adverse events associated with Gd-DTPA by using plain MRI.

The aim of the study reported here was to determine whether plain MRI-based findings are effective in evaluating joint inflammation and damage in early-stage RA in comparison to Gd-DTPA-enhanced MRI-based findings. Our results suggest that plain MRI is a sufficiently sensitive diagnostic tool to evaluate bone lesions, but that synovitis determined by plain MRI-based findings may on occasion appear as a false-positive, especially at sites where synovitis is mild.

Patients and methods

Patients

The Early Arthritis Clinic opened in 2001 as part of the Unit of Translational Medicine of the Department of Immunology and Rheumatology of the Graduate School of Biomedical Sciences of Nagasaki University. It is a regional center for the treatment of arthritis, with patients from the whole western part of Japan, Nagasaki Prefecture (approx. 450,000 inhabitants) being referred there for treatment. For our study, we recruited 51 early-stage RA patients from this clinic. The disease status of these patients was formally confirmed by a rheumatologist in our department, and a diagnosis of RA was based on the 1987 criteria for RA of the American College of Rheumatology (ACR) [10]. Baseline clinical manifestations and variables included sex, age, localization of arthritis, morning stiffness, number of tender joints, number of swollen joints, C-reactive protein level (CRP; measured by latex turbidimetric immunosorbent assay; Daiichi Pure Chemicals, Fukuoka, Japan), immunoglobulin M-rheumatoid factor (IgM-RF) positivity (measured by latex-enhanced immunonephelometric assay; cut-off value 14 IU/ml; Dade Behring, Marburg, Germany), positive status for anti-cyclic citrullinated peptide (CCP) antibodies (measured by enzyme-linked immunosorbent assay; cut-off value 4.5 U/ml; DIASTAT Anti-CCP; Axis-Shield, Dundee, UK), HLA-DRB1 genotyping, and MRI findings for both the wrists and finger joints, as previously described [5–8, 11]. All variables were examined on the same day, as previously reported [5–8, 11]. Each patient provided a signed consent form to participate in the study, which was approved by the Institutional Review Board of Nagasaki University.

MRI of wrists and finger joints

Magnetic resonance scan images of both the wrists and finger joints were acquired using a 1.5 T system (Signa; GE Medical Systems, Milwaukee, WI) with an extremity coil. T1-weighted spin-echo (TR 450 ms, TE 13 ms) images, short-time inversion recovery (STIR; TR 3000 ms, TE 12 ms, TI 160 ms) images, and Gd-DTPA-enhanced images were simultaneously acquired. The images were evaluated for bone edema, bone erosion, and synovitis in 15 sites in each finger and wrist: the distal radioulnar joint, the radiocarpal joint, the midcarpal joint, the first carpometacarpal joint, the second-fifth carpometacarpal joints (together), the first–fifth metacarpophalangeal joints, and the first–fifth proximal interphalangeal joints (PIP joints) separately (a total of 30 sites in both hands), as recently reported [5–8, 11]. The presence of synovitis, bone edema, and bone erosion was evaluated according to the methods described by Lassere et al. [12] and Conaghan et al. [13], by two experienced radiologists (M.U. and A.F.), and decisions were reached by consensus, as previously described [5–8, 11]. Since the focus of our study was to compare MRI-based findings and Gd-DTPA-enhanced MRI-based findings in terms of their accuracy in determining synovitis and bone change, we included bone edema and bone erosion as bone lesions in our study. Gd-DTPA-enhanced images were obtained by intravenous injection of 0.1 mmol/kg of Gd-DTPA (Magnevist; Bayer Schering Pharma, Berlin, Germany). A dynamic study was performed to evaluate the vascularity of the affected joints as a rate of enhancement (E-rate), which was determined by examining coronal sections taken at 4-s intervals over a 150-s time period with fast spoiled gradient recalled acquisition in the steady state (SPGR) sequences, as previously described [5–8, 11].

Comparison of plain MRI-based findings and Gd-DTPA-enhanced MRI-based findings

Gd-DTPA-enhanced MRI-based findings are the gold standard for evaluating joint inflammation and damage by MRI in RA [1]. Thus, we assumed that Gd-DTPA-enhanced MRI-based findings represented "true" lesions and subsequently calculated the accuracy of plain MRI-based findings, comparing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Statistical analysis

Differences between the groups shown in Table 4 were examined for statistical significance using the Mann–Whitney U test. A P value of <0.05 was taken to indicate a statistically significant difference.

Results

Patient characteristics

Table 1 shows the baseline characteristics of the 51 patients with RA enrolled in our study. Since the median disease duration from the onset of articular manifestations to entry was 5 months, this study population was considered to have early-stage RA. The median Genant-modified Sharp score of the 51 patients at baseline was 0.49, which also identifies them as early-stage RA patients. The rates of seropositivity of IgM-RF and anti-CCP antibodies were 62.7 and 74.5%, respectively, and the rates of carriership of the HLA-DRB1*0405 allele and HLA-DRB1*shared epitope (SE) allele were 44.0 and 56.0%. These characteristics of autoantibodies and HLA-DR typing indicate that our study population manifested typical RA characteristics.

Synovitis and bone lesions of the wrists and finger joints of both hands according to plain MRI-based findings and Gd-DTPA-enhanced MRI-based findings

Among the 1530 sites of interest, we were able to evaluate synovitis in 1416 sites on both plain MR and Gd-DTPA-enhanced MR scan images. Synovitis was considered positive in 65.6% of sites (929/1416) according to plain MRI-based findings, but was not found in 316 of these 929 sites by Gd-DTPA-enhanced MRI-based findings

Table 1 Demographic features of 51 early-stage rheumatoid arthritis patients

Demographic feature	Value
Gender (M:F, % F)	8:43 (84.3%)
Age (years)	52 (19–80)
Duration (months)	5 (1–28)
Distribution of arthritis	
Symmetric (%)	82.4
Only upper extremities (%)	27.5
Both upper and lower extremities (%)	72.5
Genant-modified Sharp score	0.49 (0–8.58)
Positivity of IgM-RF (%)	62.7
IgM-RF (IU/ml)	18.0 (4.5–395)
Positivity of anti-CCP antibodies (%)	74.5
Anti-CCP antibodies (IU/ml)	24.3 (0.6–2115.3)
Positivity of CRP (%)	70.0
CRP (mg/dl)	1.14 (0.03–11.13)
Carriership of HLA-DRB1*0405 (%)	44.0 (diploid: 8.0%)
Carriership of HLA-DRB1*shared epitope (%)	56.0 (diploid: 8.0%)

Values are given as the median with the range in parenthesis, unless otherwise stated

M Male, *F* female, *IgM* immunoglobulin M, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *CPR* C-reactive protein

Table 2 Comparison of plain MRI-based findings to Gd-DPTA-enhanced MRI-based findings

MRI findings	Gd-enhanced MRI		Total
	Synovitis (+)	Synovitis (−)	
Synovitis			
Plain MRI			
Synovitis (+)	613	316	929
Synovitis (−)	175	312	487
Total	788	628	1416
Bone lesions			
Plain MRI			
Bone lesions (+)	92	9	101
Bone lesions (−)	22	1378	1400
Total	114	1387	1501

Synovitis were evaluated in 1416 sites and bone lesions were evaluated in 1501sites as described in Patients and methods

Gd-DPTA Gadolinium–diethylenetriamine pentaacetic acid, *MRI* magnetic resonance imaging

Table 3 Sensitivity, specificity, PPV, NPV and accuracy of synovitis and bone lesions according to the plain MRI-based findings[a]

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Synovitis	77.8	49.7	66.0	64.1	65.3
Bone lesions	80.7	99.4	91.1	98.4	97.9

PPV Positive predictive value, *NPV* negative predictive value

[a] Gd-DTPA enhanced MRI-based findings were considered as gold standard; the accuracy of plain MRI-based findings were compared with Gd-DTPA-enhanced MRI-based findings

(Table 2). These data indicate that some synovitis that appears positive on a plain MR image scan is, in fact, false-positive. Bone lesions were visualized in 1501 sites by both plain and Gd-DTPA-enhanced MRI. In contrast to synovitis, the false-positive rate of bone lesions based on plain MRI findings was very low compared with that based on Gd-DTPA-enhanced MRI findings (Table 2). The rates of sensitivity, specificity, PPV and negative predictive value (NPV), and the accuracy of synovitis and bone lesion readings according to plain MRI were determined (Table 3).

The E-rate in sites of false-positive synovitis was significantly low compared with that in sites of true-positive synovitis

For the purposes of our study, the sites where plain MR scan images were positive for synovitis and Gd-DTPA-enhanced MR scan images were negative were considered to be false-positive sites; the sites for which positive results were obtained using both MRI imaging techniques were considered to be true positive sites. The severity of synovitis was compared by the E-rate of Gd-DTPA-enhanced MRI. As shown in Table 4, the E-rate of false-positive synovitis sites was significantly low compared with that of the true positive sites.

Table 4 Comparison of E-rate in sites of false-positive synovitis with sites of true-positive synovitis

MRI findings	N (sites)	E-rate (mean ± sd, median, range)	*P*-value
A. True positive; plain (+), enhanced (+)	366	8.1±5.1 (6.9, 1.2 – 50.1)	
B. False negative; plain (-), enhanced (+)	57	6.8 ±2.2 (6.5, 3.4 – 14.6)	N.S.
C. False positive; plain (+), enhanced (-)	121	5.7±2.2 (6.0, 1.4 – 14.5)	§
D. True negative; plain (-), enhanced (-)	298	5.5±1.7 (5.5, 1.4 – 12.3)	N.S.

§ | § | § | §

We compared every E-rate by Mann–Whitney *U* test. *P* values are as follows: A vs B, 0.19; A vs C, 9.2×10^{-10}; A vs D, 5.2×10^{-8}; B vs C, 0.00096; B vs D, 5.3×10^{-6} and C vs D, 0.20. It is interesting to note that E-rate of false-negative synovitis sites tended to be low, however, there is no statistical significance as compared with true-positive sites (see A vs B). E-rate of false-negative synovitis sites was high as compared with false-positive synovitis sites (see B vs C)

§ *P* value <0.0001

Discussion

Recent reviews have reported that plain MRI-based findings of bone lesions can be substituted for Gd-DTPA-enhanced MRI-based findings, although Gd-DTPA enhancement is recommended for the evaluation of synovitis [1]. Since the median disease duration from the onset of articular manifestations to entry in the 51 patients of our study cohort was 5 months, we suggest that our data reflect primarily rheumatoid joint damage, rather than secondary changes due to osteoarthritis. However, there have been few precise comparisons of plain MRI-based findings and Gd-DTPA-enhanced MRI-based findings; i.e., both plain and Gd-DTPA-enhanced sequences of multiple sites in both hands examined simultaneously. Ostergaard et al. reported that Gd-DTPA injection is not important to qualify the MRI scores of bone erosion and bone edema, whereas it is indispensable to diagnose synovitis [14].

Our data also show that plain MRI-based findings are not sufficient alone to evaluate the presence of synovitis. The severity of synovitis, as determined by the E-rate in dynamic Gd-DTPA-enhanced MR scan images, is low in false-positive synovitis sites compared with true-positive

sites. We speculate that cartilage, synovial fluids, or fibrous tissues may be interpreted as synovial hyperplasia in these cases, and we must be aware of the superiority of Gd-DTPA-enhanced MRI over plain MRI in evaluating synovitis, especially in the case of less active lesions. The E-rate of false-negative synovitis sites tended to be low among our patients; however, there was no statistical significance relative to true-positive synovitis sites. Accordingly, the E-rate of false-negative synovitis sites was high as compared with that of false-positive synovitis sites. Since a previous study demonstrated that the E-rate of the wrist correlates with the clinical disease activity in patients with RA [15], we suggest that the E-rate could correlate well with the synovitis score based on the RA MRI scoring system (RAMRIS). Consequently, findings from Gd-DTPA-enhanced MRI are crucial to qualify the presence of synovitis correctly.

Nevertheless, plain MRI is an effective tool for evaluating bone lesions of the wrists and finger joints since false-positivity is very low for this evaluation. In addition to the wrists and metacarpophalangeal joints, we identified three PIP joints as being positively associated with bone lesions out of 114 sites which were identified by Gd-enhanced MRI. There was no false-positive result by plain MRI in these three PIP joints, indicating that plain MRI is able to accurately detect the bone lesions of smaller joints of PIP joints. A recent observation (unpublished data) by our group indicates that the E-rate of sites with bone lesions is significantly high compared with that of those without bone lesions [15]. These data suggest that synovial inflammation is obvious in bone lesion sites and, therefore, that false-positivity is low in these areas.

In summary, our present data confirm the recent results of Ostergaard et al. [14] that bone lesions can be correctly identified by plain MRI-based findings in early-stage RA, while synovitis cannot. Based on our present results, we are currently investigating longitudinal changes in bone lesions by plain MRI of the wrists and finger joints in early arthritis patients during therapeutic interventions. These studies are warranted to establish the value of plain MRI in clinical rheumatology.

Acknowledgments This study was supported in part by a Grant from The Ministry of Health, Labour and Welfare, Japan.

Conflict of interest None.

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Mod Rheumatol (2013) 23:36–43
DOI 10.1007/s10165-012-0628-7

ORIGINAL ARTICLE

Musculoskeletal ultrasonography assists the diagnostic performance of the 2010 classification criteria for rheumatoid arthritis

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Received: 1 February 2012 / Accepted: 2 March 2012 / Published online: 3 April 2012

Abstract
Objective We investigated whether musculoskeletal ultrasonography (MSKUS) assists the diagnostic performance of the 2010 rheumatoid arthritis (RA) classification criteria.
Methods Sixty-nine early arthritis patients were consecutively enrolled. None of the patients had been treated. In MSKUS of bilateral wrist and finger joints from 22 sites, the findings obtained by gray-scale and power Doppler (PD) assessment were graded on a semiquantitative scale from 0 to 3. Plain magnetic resonance imaging (MRI) of both wrist and finger joints was also examined. Diagnosis of RA was defined by the initiation of disease-modifying antirheumatic drugs within the first 3 months. The diagnostic performance of the patients was evaluated at entry using 2010 RA classification criteria in conjunction with MSKUS.
Results The indispensable MSKUS finding for differentiating RA was the presence of a PD grade 2 or 3 that was superior to 2010 RA classification criteria or MRI-proven bone edema. We propose that the decision tree algorithm of 2010 RA classification criteria with PD grade 2 or 3 reveals the best discriminative ability.
Conclusion MSKUS, especially with a strong PD signal, is very useful to assist the diagnostic performance of the 2010 RA classification criteria in the early recognition of RA.

Keywords Rheumatoid arthritis · 2010 RA classification criteria · Ultrasonography · Power Doppler · MRI

Abbreviations

ACPA	Anticyclic citrullinated peptide antibody
ACR	American College of Rheumatology
CRP	C-reactive protein
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
Gd-DTPA	Gadolinium-diethylenetriamine pentaacetic acid
GS	Gray-scale
IP	Interphalangeal
MCP	Metacarpophalangeal

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MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MSKUS	Musculoskeletal ultrasonography
NPV	Negative predictive value
PD	Power Doppler
PIP	Proximal interphalangeal
PPV	Positive predictive value
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SJC	Swollen joint counts
T2T	Treat to target
TJC	Tender joint counts

Introduction

Early diagnosis and the treat to target (T2T) strategy are now indispensable for managing rheumatoid arthritis (RA) [1]. Application of the T2T strategy using the tight control approach in patients with RA, especially those with early-stage RA, has been shown to improve RA outcomes [1, 2]. Thus, the early recognition of RA is a great benefit in managing patients with RA. The 1987 American College of Rheumatology (ACR) classification criteria for RA [3] are not designed for early classification of RA. Consequently, to identify patients with erosive arthritis early, a task force of experts from both the ACR and the European League Against Rheumatism (EULAR) derived new classification criteria [4]. These new criteria, the 2010 RA classification criteria, have been verified to classify patients early as having RA more efficiently than the 1987 criteria; however, a substantial population is not still classified as having RA, even by the 2010 RA classification criteria [4].

Although physical examination is still the gold standard by which to identify the presence of arthritis [4], it has come to be apparent that modern imaging techniques such as musculoskeletal ultrasonography (MSKUS) and magnetic resonance imaging (MRI) are more sensitive than physical examination for detecting joint injury in patients with RA, especially early-stage RA [5–9]. MSKUS is well tolerated and can image a large number of joints at multiple time points over a relatively short period of time [10, 11]. Varying kinds of joint injury, including synovitis, tenosynovitis, and bone erosion, can be recorded by gray-scale (GS) and power Doppler (PD) [5–8, 10–13]. We recently reported the utility of PD to reflect clinical disease activity as well as serum biomarkers in patients with RA [14].

We speculated that the detection sensitivity for synovitis would be increased if MSKUS was routinely incorporated into clinical practice for patients with early arthritis. The objective of the study reported here was to evaluate whether the findings of MSKUS, in comparison with MRI, assist the diagnostic performance of the 2010 RA classification criteria.

Materials and methods

Patients

Sixty-nine early arthritis patients suspected of having RA were consecutively recruited. Patients who could be classified as non-RA at first visit were excluded. In addition, we excluded patients who had experience with disease-modifying antirheumatic drugs (DMARDs), including biologics and glucocorticoids. All patients were recruited from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, and the Department of Internal Medicine, Nagasaki Municipal Hospital, from May 2010 through February 2011. The duration from the appearance of symptoms to entry into the study in these 69 patients was <1 year. Patients gave their informed consent to be subjected to the protocol that was approved by the Institutional Review Board of Nagasaki University. This study was a prospective single-center observational study. Follow-up periods were at least 6 months.

Clinical and laboratory assessment

A clinical diagnosis of RA was comprehensively made by Japan College of Rheumatology (JCR)-certified rheumatologists (AK, HN, SY, and KE) using clinical histories, physical findings, blood tests including rheumatoid factor (RF) (Dade Behring, Marburg, Germany; cutoff value, 14 IU/ml), anticyclic citrullinated peptide antibodies (ACPA) (DIASTAT Anti-CCP, Axis-Shield, Dundee, UK; cutoff value, 4.5 U/ml), C-reactive protein (CRP) (Eiken Chemical Co., Ltd., Tokyo, Japan), erythrocyte sedimentation rate (ESR), matrix metalloproteinase 3 (MMP-3) (Daiichi Pure Chemicals, Fukuoka, Japan), 2010 RA classification criteria, plain radiography, ultrasound (US) findings, and MRI findings. All patients underwent the examinations except for MRI every 1–3 months. If JCR-certified rheumatologists introduced DMARDs within the first 3 months according to the above information, patients are diagnosed as having RA. Therefore, not only 2010 RA classification criteria but other information, such as MSKUS, MRI, and clinical course, are actually involved in these processes.

US examination

Each patient underwent a US assessment on the same day as the clinical evaluation by a JCR-certified rheumatologist

(SK), who was blinded to the clinical and laboratory findings. Images from all the examinations were stored, and the US scoring reliability was examined in randomly selected patients at the end of the study. This assessment was carried out by JCR-certified rheumatologists (SK, TS, AO, and TO) with consensus. A systematic multiplanar GS and PD examination of 22 joints was performed with the same scanner (TOSHIBA AplioXG) using a multifrequency linear transducer (12 MHz). The US score comprised the following 22 joints: bilateral wrists (intracarpal, radiocarpal, and ulnocarpal recesses) and finger joints, including the first through fifth metacarpophalangeal (MCP) joints, the first interphalangeal (IP) joint, and the second to fifth proximal interphalangeal (PIP) joints (dorsal recess). Flexor tendons of fingers and six components of extensor tendons of wrists were scanned. All joint regions were sonographically examined in a standardized manner according to the European League Against Rheumatism (EULAR) guidelines [13]. These are the same sites at which MRI has been used to examine patients with early arthritis, as we previously described [9, 15]. US examination of each patient took about 30 min, including documentation.

Each joint was scored for GS and PD on a semiquantitative scale [16] (synovial hypertrophy in GS: grade 0 = absence, no synovial thickening; grade 1 = mild, minimal synovial thickening filling the angle between the periarticular bones without bulging over the line linking the tops of the bones; grade 2 = moderate, synovial thickening bulging over the line linking the tops of the periarticular bones but without extension to at least one bone diaphysis; grade 3 = marked, synovial thickening bulging over the line linking the tops of the periarticular bones and with extension to at least one of the bone diaphyses; PD signals: grade 0 = absence, no synovial flow; grade 1 = mild, single-vessel signals; grade 2 = moderate, confluent signal in less than half of the synovial area; grade 3 = marked, signals in more than half of the synovial area) from 0 to 3, and presence or absence of tenosynovitis was noted. Tenosynovitis is defined by abnormal hypoechoic or anechoic material with or without fluid inside the tendon sheath and with positive PD signals in two perpendicular planes [17]. These scores corresponded to the maximum score for GS and PD obtained from any of the synovial sites evaluated at each joint. The sums of the GS and PD scores obtained from each joint were used as the GS score and PD score (range 0–66), respectively.

MRI examination

Plain MRI of both wrists and finger joints were acquired using a 1.5-T system (Sigma, GE Medical Systems, Milwaukee, WI, USA) with an extremity coil, as we recently described [9, 15, 18, 19]. Fifty-four patients were examined by MRI within a week of their US evaluation. T1-weighted spin-echo (TR 450, TE 13) images and short-tau inversion recovery (STIR; TR 3000, TE 12, T1 160) images were acquired simultaneously. The images were evaluated for synovitis, bone edema, and bone erosion at 15 sites in each finger and wrist at the distal radioulnar joint, radiocarpal joint, midcarpal joint, first carpometacarpal joint, second through fifth carpometacarpal joints (together), first through fifth metacarpophalangeal joints (separately), and first through fifth proximal interphalangeal joints (PIP joints) separately (for a total of 30 sites in both hands), as we recently reported [9, 15, 18, 19].

Statistical analyses

Within-group comparisons were made using Mann–Whitney's U test and the χ^2 test (Fisher's exact probability test when appropriate). The overall significance level for statistical analysis was 5 % (two-sided). P values <0.05 were considered statistically significant.

Results

Patient characteristics and diagnoses

The demographic and clinical characteristics of 69 patients are shown in Table 1. Thirty-seven patients (53.6 %) were diagnosed as having RA. Synthetic DMARDs were introduced within the first 3 months to these 37 patients. The initial treatments were methotrexate in 35 patients, sulfasalazine in one, and tacrolimus in one. Thirty-two patients (46.4 %) were diagnosed with other diseases (non-RA) during the follow-up periods, although they could not be classified as non-RA at entry. The diagnoses of these patients were osteoarthritis ($n = 8$), undifferentiated arthritis/arthropathy ($n = 7$), Sjögren syndrome ($n = 4$), polymyalgia rheumatica ($n = 2$), limited-type systemic sclerosis ($n = 2$), tenosynovitis ($n = 2$), reactive arthritis ($n = 1$), polymyositis ($n = 1$), immunoglobulin (Ig)G_4-related disease ($n = 1$), sarcoidosis ($n = 1$), adult T-cell leukemia (ATL), familial Mediterranean fever ($n = 1$), and phalangeal microgeodic syndrome ($n = 1$). The mean disease duration was approximately 4 months in both RA and non-RA patients. The swollen joint counts ($p = 0.0104$) and CRP ($p = 0.0003$) and ESR ($p = 0.0009$) values were higher in RA patients than in non-RA patients, but the tender joint counts were not different. The seropositive rates of RF (70.3 %, $p = 0.0002$) and ACPA (62.2 %, $p < 0.0001$) were significantly higher in RA than in non-RA patients. Patients with high MMP-3 were also predominantly distributed in the RA group (48.6 %, $p = 0.0432$).

Comparison of MSKUS findings between RA and non-RA patients

The MSKUS findings in RA and non-RA patients are shown in Table 2. The rates at which GS grade ≥1 ($p = 0.0005$), GS grade ≥2 ($p < 0.0001$), GS grade = 3 ($p < 0.0001$), PD grade ≥1 ($p < 0.0001$), and PD grade ≥2 ($p < 0.0001$) were present at any joint were significantly higher in RA than in non-RA patients. However, GS grade ≥1, GS grade ≥2, and PD grade ≥1 also occurred in non-RA patients, as 23 (71.9 %), 12 (37.5 %), and ten (31.3 %) patients were positive for the above grades, respectively, out of 32 non-RA patients. The occurrence of PD grade = 3 was specific to RA patients; however, it was only found in four of 37 RA patients (10.8 %). Both GS and PD scores were significantly higher in RA than in non-RA patients. The frequency of findings of tenosynovitis was prominent in the RA group, but the difference from the frequency in the non-RA group was not significant. Bone erosions were specifically detected in RA patients; however, the rate was not high (18.9 %, $p = 0.0094$). Accordingly, PD grade ≥2 at any joint is considered to be most important MSKUS findings in RA patients.

Comparison of plain MRI findings between RA and non-RA patients

The plain MRI findings in RA and non-RA patients are also shown in Table 2. As most patients with RA expressed symmetrical synovitis that was also found in non-RA patients, we could not find statistical significance in this result. As suspected, bone edema was significantly distributed in the RA group compared with the non-RA group; however, that was not so remarkable compared with MSKUS findings. Patients with MRI-proven bone erosion tended to be distributed in the RA group, but the difference did not reach statistical significance ($p = 0.0838$).

Laboratory data, MSKUS findings, MRI findings, and 2010 RA classification criteria for the diagnosis of RA

Sensitivity, specificity, and accuracy of laboratory data, MSKUS findings, MRI findings, and 2010 RA classification criteria are shown in Table 3. The presence of ACPA was the most specific laboratory data distributed in patients with RA. Surprisingly, the presence of MSKUS findings, especially the presence of PD grade 2 or 3 at any joint, was very specific in

Table 1 Demographic, clinical, and laboratory characteristics at baseline

	RA ($N = 37$)	Non-RA ($N = 32$)	P value
Age (years[a])	53.6 ± 17.2	54.5 ± 12.5	NS
Female/male (n)	28/9	26/6	NS
Durations of symptom (months[a])	4.0 ± 3.0	3.7 ± 2.9	NS
≥1.5 months/<1.5 months	31/6	24/8	NS
Tender joint counts (n[a])	7.9 ± 7.6	5.6 ± 6.9	NS
Swollen joint counts (n[a])	5.6 ± 6.9	3.4 ± 6.3	0.0104
CRP			
Positive/negative	24/13	8/24	0.0009
Value (mg/dl[a])	1.29 ± 2.94	0.40 ± 1.09	0.0003
ESR			
Positive/negative	27/10	11/21	0.0013
Value (mm/h[a])	32.2 ± 24.5	18.0 ± 20.6	0.0009
CRP and/or ESR			
Positive/negative	31/6	13/19	0.0002
RF			
Positive/negative	26/11	8/24	0.0002
Titers: >×3/≤×3	17/20	3/29	0.0083
ACPA			
Positive/negative	23/14	2/30	1.4×10^{-6}
Titers: >×3/≤×3	23/14	1/31	2.8×10^{-7}
IgM-RF and/or ACPA			
Positive/negative	27/10	9/23	0.0002
Titers: >×3/≤×3	23/14	4/28	2.5×10^{-5}
MMP-3			
Positive/negative	18/19	8/24	0.0432

Within-group comparisons were assessed with Mann–Whitney's U test and the χ^2 test (Fisher's exact probability test when appropriate)

NS not significant, *RF* rheumatoid factor, *ACPA* anti-CCP antibody, *MMP-3* matrix metalloproteinase-3

[a] Mean ± standard deviation

Table 2 Ultrasonography and MRI findings at baseline

	RA ($N = 37$)	Non-RA ($N = 32$)	P value
MSKUS			
Gray-scale			
Grade ≥1 presence/absence	37/0	23/9	0.0005
Grade 2 or 3 presence/absence	33/4	12/20	6.9×10^{-6}
Grade 3 presence/absence	21/16	1/31	1.9×10^{-6}
Total GS score (0–66)[a]	9.4 ± 7.6	3.7 ± 4.0	0.0001
Power Doppler			
Grade ≥1 presence/absence	34/3	10/22	1.7×10^{-7}
Grade 2 or 3 presence/absence	30/7	2/30	5.1×10^{-10}
Grade 3 presence/absence	4/33	0/32	0.0764
Total PD score (0–66)[a]	4.2 ± 3.7	0.6 ± 1.1	9.7×10^{-9}
Tenosynovitis			
Presence/absence	21/16	6/26	0.0013
Bone erosion			
Presence/absence	7/30	0/32	0.0094

	RA ($N = 32$)	Non-RA ($N = 22$)	P value
MRI			
Symmetrical synovitis			
Presence/absence	28/4	16/6	NS
Bone edema			
Presence/absence	15/17	4/18	0.0300
Bone erosion			
Presence/absence	9/23	2/20	0.0838

Within-group comparisons were assessed with Mann–Whitney's U test and the χ^2 test (Fisher's exact probability test when appropriate)

RA rheumatoid arthritis, *MSKUS* musculoskeletal ultrasonography, *GS* gray-scale, *PD* power Doppler, *MRI* magnetic resonance imaging, *NS* not significant

[a] Mean ± standard deviation

RA. If we considered patients to have RA in cases in which MSKUS findings showed PD grade 2 or 3, the diagnostic performance of MSKUS for RA had sensitivity 81.1 %, specificity 93.8 %, positive predictive value (PPV) 93.8 %, negative predictive value (NPV) 81.1 %, and accuracy 87.0 %. The 2010 RA classification criteria classified RA with sensitivity 59.5 %, specificity 87.5 %, PPV 84.6 %, NPV 65.1 %, and accuracy 72.5 %, suggesting that the presence of PD grade 2 or 3 may have been more specific than the 2010 RA classification criteria. In accordance with data shown in Table 2, MRI-proven bone edema could not differentiate RA from non-RA compared with PD grading.

We tried to combine 2010 RA classification criteria with the PD grade 2 or 3 rule for the clinical diagnosis of RA, and the results are shown in Fig. 1. We initially applied 2010 RA classification criteria, and if the patients did not fulfill those criteria, the PD grade 2 or 3 rule was introduced. We found that this decision tree can differentiate patients more efficiently than can the PD grade 2 or 3 rule alone.

Discussion

The authors of previous assessments of the performance of the 2010 RA classification criteria have usually tried to identify patients with RA as those who were treated with DMARDs within the first year of the follow-up period [20–23]. As of this writing, the 2010 RA classification criteria were published last year and are going to be applied in the clinical field of rheumatology. Rheumatologists tend to start DMARDs earlier in patients who are expected to develop erosive arthritis. Therefore, in this study, we considered patients to have RA if their physicians had started DMARDs within the first 3 months. This clinical setting may clarify more definitely which patients should be considered to have RA for the purpose of applying the T2T strategy that has come to be widely recommended.

Diagnostic performance of the 2010 RA classification criteria in this study was fairly good, with both the specificity and PPV around 85 %. As this was a prospective investigator-initiated clinical study, physicians were able to choose the treatment at every visit according to the clinical status of patients fulfilling the 2010 RA classification criteria. Thus, ithe score according to the 2010 RA classification criteria at each visit may be directly involved in the physician's decision, which associated with the increment of specificity and PPV of the 2010 RA classification criteria. However, the levels of other components, such as sensitivity, NPV, and accuracy, were not high, indicating that additional procedures may be necessary to assist the

Table 3 Performance of laboratory data, ultrasonography findings, and 2010 rheumatoid arthritis (RA) classification criteria

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Laboratory data					
CRP (positive)	64.9	75.0	75.0	64.9	69.6
ESR (positive)	73.0	65.6	71.1	67.7	69.6
RF (positive)	70.3	75.0	76.5	68.6	72.5
ACPA (positive)	62.2	93.8	92.0	68.2	76.8
MMP-3 (positive)	48.6	75.0	69.2	55.8	60.9
MSKUS					
Gray-scale; grade ≥1	100	28.1	61.7	100	66.7
Gray-scale; grade 2 or 3	89.2	62.5	73.3	83.3	76.8
Gray-scale; grade 3	56.8	96.9	95.5	66.0	75.4
Power Doppler; grade ≥1	91.9	68.8	77.3	88.0	81.2
Power Doppler; grade 2 or 3	81.1	93.8	93.8	81.1	87.0
Power Doppler; grade 3	10.8	100	100	49.2	52.2
Tenosynovitis (positive)	56.8	81.3	77.8	61.9	68.1
Bone erosion (positive)	18.9	100	100	51.6	56.5
MRI					
Symmetrical synovitis (positive)	87.5	27.3	63.6	60.0	63.0
Bone edema (positive)	46.9	81.8	78.9	51.4	61.1
Bone erosion (positive)	28.1	90.9	81.8	46.5	53.7
2010 RA classification criteria	59.5	87.5	84.6	65.1	72.5

RF rheumatoid factor, *ACPA* anti-CCP antibody, *MMP-3* matrix metalloproteinase-3, *MSKUS* musculoskeletal ultrasound, *PPV* positive predictive value, *NPV* negative predictive value, *MRI* magnetic resonance imaging

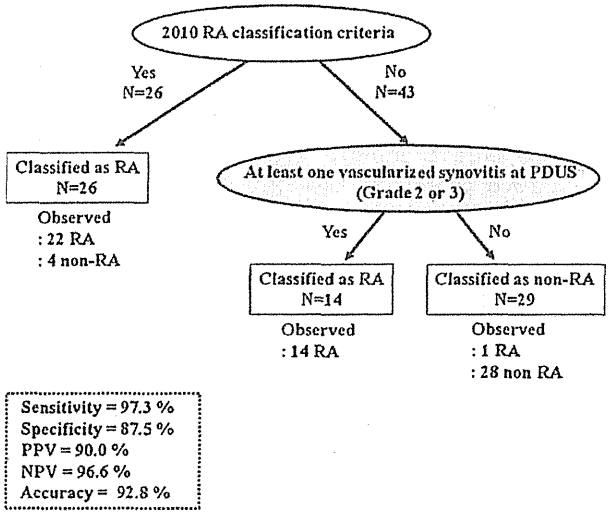

Fig. 1 Decision tree algorithm for diagnosis of early arthritis patients by 2010 rheumatoid arthritis (RA) classification criteria in conjunction with power Doppler PD grade 2 or 3; 2010 RA criteria were initially applied to 69 patients. If the patients fulfilled the criteria, they were classified as having RA (26 patients). PD grade 2 or 3 rule was applied for the remaining 43 patients. This tree algorithm classified patients as having RA at sensitivity 97.3 %, specificity 7.5 %, positive predictive value (PPV) 90.0 %, negative predictive value (NPV) 96.6 %, and accuracy 92.8 %

diagnostic performance of the 2010 RA classification criteria.

In this regard, we focused on MSKUS, as it is more sensitive and reliable than clinical examination for detecting joint injury in patients with RA [5–8]. Synovitis, tenosynovitis, and bone erosion are the major joint injuries that are frequently found in patients with RA examined by MSKUS [5–8, 10–13]. GS determines the hypertrophy of synovial tissues, whereas PD identifies vascularity [5–8, 10–13]. In our study, PD grade, especially grade 2 or 3, was highly specific in patients with RA. These data are consistent with the previous findings that the synovial vascularity determined by PD reflects RA disease activity more efficiently than do GS findings [24, 25]. The levels of statistical components were even better than those of the 2010 RA classification criteria, indicating that the presence of severe and active synovial inflammation detected by PD may deeply affect physicians' decisions to start DMARDs.

Although the US examiner was always blinded to the clinical and laboratory findings of patients in this study, physicians could take into consideration the results of US for the choice of DMARDs at each point. Therefore, it could also be said that PD overestimates the presence of RA and thus influences the initiation of or choice of DMARDs that was directly associated with our data. As for

MRI, the presence of bone edema is thought to be the most suitable indicator for a clinical diagnosis of RA. These results are consistent with our previous report that bone edema is able to predict the development of RA that fulfills the 1987 classification criteria from patients with early arthritis more efficiently than symmetrical synovitis and bone erosion [15]. As physicians judge patients as having RA based on findings of not only MSKUS but also MRI, we could state that PD grade 2 or 3 is superior to bone edema on plain MRI for making a clinical diagnosis of RA. If we obtain gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)-enhanced MRI instead of plain MRI, bone edema may be more significantly involved in RA diagnosis. In our previous study, we found that the detection sensitivity of bone edema on plain MRI is 30 % less than that with Gd-DTPA-enhanced MRI [15]. We therefore propose a tree algorithm for clinical RA diagnosis that combines the 2010 RA classification criteria and PD, as shown in Fig. 1. This kind of approach can also be applied in patients with spondyloarthropathy, indicating that Amor's criteria in conjunction with vascularized enthesis bring good results [26]. Accordingly, our data identify that the tree algorithm shown in Fig. 1 can classify more patients as having RA at a high discriminative value compared with the 2010 RA classification criteria or PD alone, supposing more patients received the chance of early introduction of DMARDs. Our data may also indicate that the combination of physical examination and serology with a sensitive imaging technique, such as MSKUS, is the best way to identify erosive disease early. Filer et al. [7] reported that a combination of Leiden score, but not the 2010 RA classification criteria, with MSKUS-proven synovitis improved in clinical RA diagnosis. Our data may follow that result. Long-term follow-up and larger studies are warranted to confirm that MSKUS, especially PD, in combination with the 2010 RA classification criteria, is valuable for early identification of patients with erosive RA

Conflict of interest None.

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