SCIENTIFIC ARTICLE

Metalloproteinase Gene Expression Correlates With Clinical Outcome in Dupuytren's Disease

Phillip Johnston, MB BChir, Debbie Larson, BSc, Ian M. Clark, PhD, Adrian J. Chojnowski, MB BChir

Purpose We have previously demonstrated that gene expression levels of matrix metalloproteinases (MMPs), related metalloproteinases "a disintegrin and metalloproteinase with thrombospontin motifs" (ADAMTSs), and tissue inhibitors of metalloproteinases (TIMPs) differed when comparing palmar fascia from 19 patients with Dupuytren's disease (DD) with 19 disease-free controls. We undertook to investigate whether the extent of this altered gene expression was related to clinical outcome.

Methods All the patients with DD were followed up for an average of 14 months from their primary fasciectomy. Clinical outcome was scored by measuring range of motion to assess total extension deficit (fixed flexion deformity [FFD] of the affected digit), total further flexion, and grip strength, and using 3 validated outcome scores: the Disability of Arm, Shoulder and Hand (DASH) questionnaire, the Michigan Hand Questionnaire (MHQ), and the Vancouver Scar Scale (VSS).

Results We found a considerable correlation between levels of gene expression of several of the MMPs (MMP2, MMP13, MMP14, MMP16, MMP 19) and ADAMTSs (ADAMTS2, ADAMTS4, ADAMTS5, ADAMTS14, ADAMTS16) and the recurrence of FFD over the follow-up period. The expression of all these genes had been shown to be increased in DD samples compared with controls. We also found that the expression levels of several of these genes correlated with 2 other preoperative measurements, total further flexion (digital roll-up) and grip strength.

Conclusions These findings suggest that gene expression levels of key MMPs and ADAMTSs could be used to predict 1-year clinical outcome in terms of recurrent FFD of the affected finger following fasciectomy for DD. This implies that knowledge of these expression levels could be used to direct appropriate surgical and adjuvant intervention for DD. This study also provides further evidence to support the functional link between metalloproteinase gene expression and symptomatic progression or recurrence. *(J Hand Surg 2008;33A:1160–1167.*

Type of study/level of evidence Prognostic IV.

Key words: ADAMTS, Dupuytren's Disease, gene expression, MMP, TIMP.

Dupuytren's disease is a fibroproliferative disease affecting the palmar fascia, often resulting in contracture causing functional disability in the affected hand.[1] Surgery is the most widely used treatment modality, with procedures ranging from percutaneous fasciotomy to dermofasciectomy and skin grafting.[2] Alternative methods of treatment have been reported as less successful and are often used as an

From the Department of Orthopaedics, Addenbrooke's Hospital, Cambridge, UK; Department of Occupational Therapy, Norfolk & Norwich Hospital, Norwich, UK; School of Biological Sciences, University of East Anglia, Norwich, UK.

Received for publication August 16, 2007; accepted in revised form April 2, 2008.

Support was received from Action Arthritis, a registered charity who provided funds towards running costs of the project (consumables only).

Corresponding author: Phillip Johnston, MB BChir, Department of Orthopaedics, Box 37, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK; e-mail: phillip.johnston@nhs.net.

0363-5023/08/33A07-0021$34.00/0
doi:10.1016/j.jhsa.2008.04.002

adjunct to surgery rather than in its place.[3] Disease progression is seen as inevitable in the long term rather than as a complication or failure of surgery, but it is extremely variable and often unpredictable.[4] The primary cell thought to be responsible for the alteration in architecture of the palmar fascia is the myofibroblast,[5] although it remains unclear whether the fascial fibroblasts are activated *in situ* (intrinsic theory) or whether active myofibroblasts are recruited from more distant sites after the disease state is established (extrinsic theory).

The observation that use of broad-spectrum matrix metalloproteinase (MMP) inhibitors in clinical trials aimed at reducing local invasion and distant metastasis in certain malignancies was associated with a (fibrotic) musculoskeletal syndrome[6] resembling DD and frozen shoulder[7] kindled the concept that altered activity of MMPs might be important in the pathogenesis of DD. We have previously reported a case-control series detailing the extent of the alteration in gene expression of MMPs, ADAMTSs, and TIMPs in DD.[8] We found that the gene expression levels of several key proteolytic enzymes were considerably increased in samples of palmar fascia from patients with DD compared to patients without the condition. This work has in part been corroborated by other workers,[9,10] using quantitative techniques to measure the gene expression of all of the MMPs, ADAMTSs, and TIMPs.

As a subsequent study, we set out to investigate whether the extent of this alteration in gene expression level was related to clinical parameters in our cohort of patients with DD. If there was a correlation between levels of gene expression and clinical parameters, then this might be useful as a marker of outcome for future patients, providing a novel technique to use for prognosis, and perhaps to direct adjuvant therapy in cases thought likely to recur more rapidly.

MATERIALS AND METHODS

All surgery was performed in our orthopedic unit with approval of the local research ethics committee, and all patients provided informed consent. The procedures were all performed by, or under close supervision of, 1 of 3 consultant hand surgeons. In all cases, patients had simple fasciectomy for primary DD, using Bruner (zig-zag) incisions along the affected finger. All of the patients in the original cohort were followed up for a mean period of 14 months (range, 11–16 months). Preoperative, early postoperative (approximately 3 months), and final postoperative scores were obtained for several clinical parameters.

Range of motion of the affected digit was calculated from 2 measurements: (1) total extension deficit (equivalent to the degree of FFD of the finger), calculated from the sum of the fixed flexion at the metacarpophalangeal and proximal and distal interphalangeal joints; and (2) total further flexion, calculated from the sum of maximum flexion at the metacarpophalangeal and proximal and distal interphalangeal joints. These angles were measured using a standard goniometer placed over the dorsal surface of the digit around the joint in question according to standard practice. Grip strength was measured in newtons (N) using a hydraulic hand dynamometer (North Coast Medical, Morgan Hill, CA).

The DASH questionnaire,[11] a validated self-administered tool, was used. It consists of 30 questions ranging from functional to psychological to generate a score from 0 to 100 (where 0 is no disability and 100 is total). The MHQ[12] was also used. It is a validated outcome measurement tool that is side-specific. From 25 unilateral and 12 bilateral questions, including hand function, work performance, and cosmetic appearance, it generates a score from 0 to 100 (where 0 is complete disability and 100 is none). There is no accepted scar scoring tool in use for DD; we therefore used a scale validated for scoring scars caused by burns, the VSS,[13] which scores the scar for pigmentation, height, vascularity, and pliability, providing a maximum of 18 for a scar that is highly symptomatic.

The gene expression measurement method has been previously described in detail.[8] In brief, fascial samples were snap-frozen in liquid nitrogen immediately after harvesting. Samples were homogenized, and the RNA was extracted using a spin column (RNeasy MiniKit, QIAGEN, Crawley, UK). This was reverse-transcribed into complementary cDNA, and gene expression was assessed using real-time RT-qPCR (ABI Prism 7700 sequence detector, Applied Biosystems, Foster City, CA). As a quality control measure, samples whose 18S rRNA PCR cycle threshold (C_T) values fell ± 1.5 from the median value were discarded from further analysis. Using previously described and validated primers and probes for all the known MMPs, TIMPs, and ADAMTSs,[14,15] the relative expression levels for all of these could be determined for each of the subjects.

Data were collected and input into a spreadsheet (Microsoft Excel 2003, Microsoft Corporation, Redmond, WA) and were analyzed using SPSS Version 12.0.2 (SPSS Inc., Chicago, IL). In view of the relatively small numbers of patients in the cohort, nonparametric tests were used in the statistical analyses; correlations were assessed using the Spearman rank test.

TABLE 1. Basic Patient Demographics

Demographic	N = 19
Age in years (range)	68.2 (42.5–85.4)
Gender	Male = 16
Finger affected	D5 = 6; D4 = 7; Multiple = 6
Stage	Stage 2 = 4
	Stage 3 = 8
	Stage 4 = 7
Smoker	9
Epilepsy	1
Diabetes	1
Excessive alcohol consumption	4
Family history	3

RESULTS

Twenty patients were originally recruited into the study. The basic demographic data for the cohort are shown in Table 1. The majority of patients were men, and nearly half were smokers. A minority recalled a positive family history, although this failure to identify affected family members has been noted in previous epidemiological studies of DD. Due to the quality-control step in the gene expression level measurement, only 19 patients' tissue from each group were analyzed (1 sample from each group fell outside the accepted range for 18S rRNA C_T in the PCR). Similarly, not all the data for the pre- and postoperative clinical scores were available for inclusion.

In our original report of the gene profile for these groups,[8] we included gene expression data for all the MMPs, TIMPs, and ADAMTSs. Because the samples from patients with DD had been separated macroscopically into cord and nodule, we were also able to look at differences in gene expression levels within the same patient from more active (nodule) or inactive (cord) areas of the DD tissue. We have previously reported several differences between these 2 groups. However, for ease of analysis and because in general the gene expression differences between the DD cases and the control group were most marked in nodule samples, we elected to exclude the gene expression levels from cord samples from this current study. We did find some evidence for a difference in gene expression levels between men and women in a few of the genes (MMP16, TIMP2, ADAMTS3, and ADAMTS5), but we did not find a difference in clinical parameters between the genders.

TABLE 2. Measurement Data and Outcome Scores for Cohort After 3 Months (Interim Review) and 14 Months (Final Review)

Measurement	Time Period	Mean	Standard Deviation	N
Fixed flexion (°)	Preoperative	73	38	17
	Interim follow-up	28	32	15
	Final follow-up	30	20	16
Further flexion (°)	Preoperative	236	29	17
	Interim follow-up	230	30	15
	Final follow-up	238	24	16
Grip strength (N)	Preoperative	32.6	12.9	7
	Interim follow-up	25.6	10.4	12
	Final follow-up	33.4	13.9	16
DASH	Preoperative	24	20	17
	Interim follow-up	15	12	14
	Final follow-up	8	8	16
MHQ	Preoperative	58	16	17
	Interim follow-up	75	16	12
	Final follow-up	87	12	16

The numbers of patients studied and their ranges of finger movement and grip strength are shown in Table 2. The change in FFD (change in total extension deficit) is also shown graphically for 16 of the 19 patients in Figure 1 (data for the remaining 3 were lost). The majority of patients (15 of the 16) achieved a marked improvement in FFD following surgery at the initial follow up. One patient developed complex regional pain syndrome (type 1) and was worse at the initial postoperative review than he had been before surgery, although he was found to have improved by the final follow-up. Between the interim and final follow-up time points, 5 patients showed no notable change in FFD and 3 patients showed a further improvement (including the patient with complex regional pain syndrome). However, 8 patients subsequently were found to have developed some recurrence of this FFD at the final postoperative review (mean 18°, SD 14°). DASH, MHQ, and VSS scores are also shown in Table 2. The minimal detectable change score (the minimum change score required before an individual can be considered to have changed by more than day-to-day variability) for the DASH is generally accepted to be 15 points.[16]

Correlations were assessed between the clinical outcomes and gene expression levels of MMPs, ADAMTSs, and TIMPs previously identified as significantly altered in DD.[8] The values used were the trans-

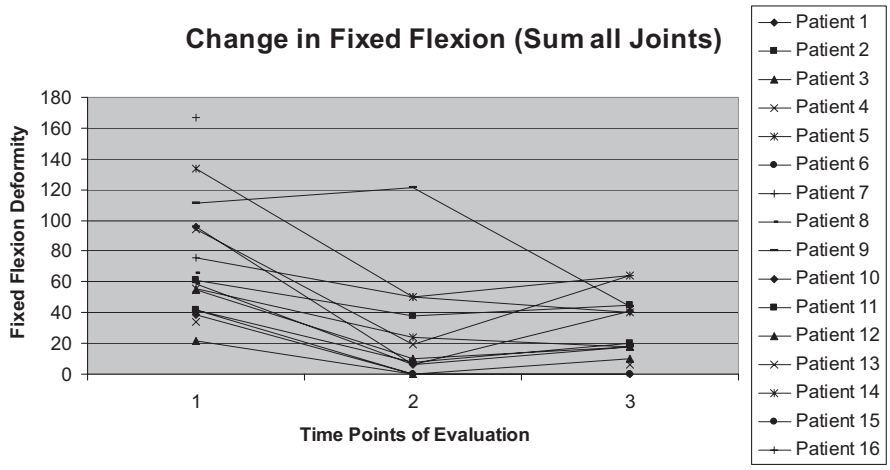

FIGURE 1: Graph of individual patients' change in fixed flexion over time. Time points: 1, preoperative; 2, interim postoperative; 3, final postoperative. Data include only 16 patients' measurements (3 were unavailable).

TABLE 3. Correlation Analyses* for Change in Fixed Flexion Versus Gene Expression Data

Gene	Change Between Interim and Final Follow-Up p Value (R Value) (N = 15)	Change Between Preoperative and Final Follow-Up p Value (R Value) (N = 16)
MMP1	.055 (0.504)	
MMP2	.007 (0.662)	
MMP11	.057 (0.501)	
MMP13	.002 (0.739)	.05 (0.498)
MMP14	.006 (0.674)	
MMP16	.018 (0.601)	
MMP19	.01 (0.639)	
MMP27		.033 (−0.533)
TIMP1	.039 (0.537)	
TIMP3	.052 (−0.510)	
TIMP4	.011 (−0.633)	
ADAMTS2	.005 (0.687)	
ADAMTS3	.045 (0.524)	
ADAMTS4	.006 (0.673)	.043 (0.511)
ADAMTS12	.032 (0.555)	
ADAMTS14	.002 (0.725)	.043 (0.511)
ADAMTS16		.047 (0.504)

*Spearman's rank correlation; R value, correlation coefficient.

formed cycle threshold (C_T) for the respective gene, normalized to the patient's measured C_T for 18S rRNA. When performing multiple hypothesis tests, often a correction is made to adjust for the risk of false positive results (type 1 error). We have not applied such a correction, to avoid creating false negative results, or a type 2 error (such a pragmatic approach is often used in profiling analyses of gene expression).

Table 3 demonstrates the metalloproteinase gene expression levels that are significantly correlated with recurrence of the flexion contracture, comparing measurements at the interim and final clinical reviews. We have not formally defined *recurrence* as a particular value of fixed flexion, instead looking at the association between change in FFD and gene expression level in any particular patient. MMP-2 (gelatinase A), MMP-

TABLE 4. Correlation Analyses* for Preoperative Total Further Flexion Versus Gene Expression Data

Gene	p Value (R Value) (N = 17)
MMP2	0.002 (0.685)
MMP7	0.014 (−0.585)
MMP11	0.032 (0.052)
MMP13	0.04 (0.503)
MMP14	0.014 (0.585)
MMP16	0.059 (0.467)
MMP19	0.008 (0.617)
TIMP1	0.079 (0.438)
TIMP3	0.019 (−0.562)
ADAMTS2	0.005 (0.646)
ADAMTS3	0.039 (0.505)
ADAMTS4	0.073 (0.445)
ADAMTS12	0.033 (0.517)
ADAMTS14	0.004 (0.655)
ADAMTS16	0.047 (0.488)
ADAMTS18	0.042 (0.498)

*Spearman's rank correlation; R value, correlation coefficient.

TABLE 5. Correlation Analyses* for Preoperative Grip Strength Versus Gene Expression Data

Gene	p Value (R Value) (N = 7)
MMP2	0.014 (0.857)
MMP7	0.052 (−0.75)
MMP14	0.003 (0.929)
MMP17	0.014 (0.857)
TIMP1	0.003 (−0.929)
TIMP2	0.003 (0.929)
ADAMTS2	0.036 (0.786)
ADAMTS3	0.036 (0.786)
ADAMTS5	<0.001 (0.964)
ADAMTS9	0.003 (0.929)
ADAMTS12	0.007 (0.893)
ADAMTS16	0.014 (0.857)

*Spearman's rank correlation; R value, correlation coefficient.

13, and MMP-14 are all enzymes capable of degrading fibrillar collagens, whereas ADAMTS-2 and ADAMTS-14 are both procollagen-N-propeptidases with a role in collagen biosynthesis (thus useful markers for collagen production). MMP-16 and MMP-19 are capable of degrading a number of extracellular matrix components and have been associated with vascular proliferation, but they have also been reported to be increased in pathological conditions, for example in osteoarthritic cartilage,[17,18] as has ADAMTS-16. ADAMTS-4 and ADAMTS-5 are aggrecan-degrading enzymes, again pivotal in extracellular matrix turnover. We found no evidence for a correlation between gene expression levels and change in FFD between pre- and interim postoperative reviews. We have therefore not included these data. This reflects that the majority (15 of 16) of patients' FFD improved after surgery (as would be hoped). The correlations were also less marked when taking overall change in FFD (from pre to final postoperative review). This reflects 2 changes in FFD: the initial improvement (in the majority) and the subsequent recurrence (in some cases).

Tables 4 and 5 show the correlations between gene expression levels and 2 of the preoperative scores, total further flexion (digital roll-up) and grip strength. Again, it can be seen that gelatinase (MMP2), collagenase (MMP13 and MMP14), MMP7, and ADAMTS expression correlates with digital roll-up, such that increased proteolysis (a marker for increased extracellular matrix turnover) is associated with improved roll-up (less digital fibrosis), whereas increased TIMP3 expression (increased fibrosis) is associated with less roll-up (negative correlation). Again, similar associations can be seen between gene expression levels and grip strength, suggesting that an increased turnover of extracellular matrix correlated with improved grip strength.

Table 6 shows the correlations between the 2 functional outcome measures used. Each appears to correlate well at individual time points of follow-up. DASH scores showed a close correlation with each other over time; a higher preoperative DASH score was predictive of a high final DASH score. We found no such correlation within the MHQ scores over time. This perhaps implies more patient subjectivity in using the DASH as an outcome measure in DD, and although, at first glance, DASH may appear to be a valid predictor of outcome (certainly as measured by DASH score), it might be difficult to separate those subjective components of the disability from DD from the objective (unlike a measure, for example, such as gene expression level). We also found strong evidence for a correlation between change in both MHQ and DASH scores when comparing preoperative and final postoperative scores ($p = .001$, $R = -0.731$) and between the change in MHQ and change in FFD ($p < .001$, $R = -0.784$).

TABLE 6. Correlation Between 2 Outcome Measures

Measure	DASH Interim*	DASH Final†	MHQ Pre Op	MHQ Interim*	MHQ Final†
DASH preoperative	p = .015 R = .654 (n = 13)	p = .003 R = .685 (n = 16)	p < .001 R = −0.788 (n = 17)	p = .034 R = −0.532 (n = 16)	p = .034 R = −0.532 (n = 16)
DASH interim*		NS	p = .042 R = −0.569 (n = 13)	p = .03 R = −0.626 (n = 12)	NS
DASH final†			NS	NS	p = .002 R = −0.721 (n = 16)
MHQ preoperative				p = 0.068 R = 0.544 (n = 12)	NS
MHQ interim*					NS

R, Spearman's rank coefficient; NS, not significant (p > .05).
*Mean 3 months after surgery.
†Mean 14 months after surgery.

This last suggests that MHQ might be of more value for objective scoring in DD.

We found no evidence for a correlation between change in total further flexion and any of the outcome scores used (probably because total further flexion did not change notably over time for each patient). The VSS at final follow-up did not correlate with levels of gene expression, nor with DASH or MHQ. This might merely represent the insensitivity of this tool to distinguish scarring in DD, or perhaps the appearance and surface characteristics of the scar is unrelated to activity deeper in the palmar structures. We found no evidence for an effect of age or gender on any of the outcome scores.

DISCUSSION

We have found several results in this study. First, we found that recurrence of FFD from the initial postoperative review until our final review at a mean of 14 months correlated with gene expression levels. In the majority of cases, this was a positive correlation—that is, the greater the gene expression, the greater the change (in the majority of cases, a worsening) in FFD between the 2 time points. The inference here is that patients with greater metalloproteinase activity (whether MMP or ADAMTS) had a greater recurrence of flexion contracture. Two genes showed a negative correlation, both TIMPs. In these, we found that greater TIMP expression correlated with a more favorable result at 14 months (less recurrent flexion contracture). This would corroborate other work that has likened DD to a tumor-like condition[19] in which greater turnover of extracellular matrix equates to greater disease activity (or in this case, greater recurrence of FFD, which might not be the same). Conversely, increased TIMP expression might counter the disease advancement effect of the proteolysis by the upregulated metalloproteinases, leading to slower or less recurrence of FFD (as we have shown). This result has never been shown before and indeed it is rare to link laboratory and clinical results in this way. It is likely that, if such a correlation is seen within a relatively small group of patients (n = 19), this result is highly notable and would only be reinforced by greater numbers.

Second, we have identified that several genes strongly correlate with other preoperative parameters; for example, preoperative grip strength and total further flexion (digital roll-up). In itself, this is of perhaps passing interest, but taken with the outcome data, this also provides an interesting insight into a genetic profile of an individual patient with DD. This again might allow formation of a prognosis for such patients and might help to discriminate between those who require simple fasciectomy for their disease from those who might benefit from a more radical primary operation. It is also noteworthy that several of the genes (MMP2, MMP14, TIMP1, and ADAMTSs 2, 3, 12, and 16) were strongly correlated to both clinical parameters, despite finding no correlation between grip strength and total further flexion (which would point away from a common factor influencing both similarly). We found no correlation comparing gene expression with change

in total flexion of the affected digit. Perhaps this is not surprising as DD is not usually associated with a reduction in flexion, and the flexion scores did not change significantly during the follow-up time period.

Third, 1 of the outcome measures employed (DASH) showed strong correlations within patients over time. In other words, the preoperative DASH scores correlated well with the interim (3-month) and final (14-month) values. Thus, from the patient's preoperative scores, it should again be possible to predict their postoperative scores (although this in part might merely reflect the subjectivity of this patient-centered outcome measure). The outcome measures were chosen because they are patient-centered, easy and quick to administer, and there is some evidence to validate their use in DD. The weak evidence for a correlation between change in FFD and DASH score probably merely reflects the need to change at least 15 points on the DASH scale for a clinically important effect (the mean starting DASH score in our series was 24). DASH and MHQ values correlated well with each other at each time point, and change in MHQ also correlated strongly with change in FFD, providing some evidence for validation of their use in DD.

MMP-13 (collagenase 3) is a metalloproteinase whose expression has been shown to be increased not only in DD but also in other pathological states, notably in osteoarthritic cartilage[17,18] and in degenerative tendinopathy.[20] MMP-14 is a membrane-bound metalloproteinase (membrane-type 1 metalloproteinase) that can also cleave collagen and has been demonstrated to be preferentially expressed at the leading edge of cells invading extracellular matrix *in vitro*[21] and might play an important role in the remodeling of the fascial extracellular matrix as the myofibroblasts migrate within it. MMP-14 also activates proMMP-2, a gelatinase that also displays collagen-degrading activity.[22] ADAMTS-2 and ADAMTS-14 are procollagen-N-propeptidases, whose activity is increased with increased collagen synthesis (such as in DD).[23] ADAMTS-4 and ADAMTS-5 are aggrecanases, the latter considered key, for example, in cartilage destruction during osteoarthritis. These enzymes can also degrade other proteoglycans such as brevican, versican, decorin, and fibromodulin.[24] A recent report demonstrates that normal palmar fascia contains mainly decorin, whereas in DD there is an accumulation of biglycan and large chondroitin sulphate and dermatan sulphate proteoglycans.[25] The fact that the expression of these genes correlates strongly with the extent of postoperative recurrence of FFD underlines the importance of both collagen metabolism and proteoglycan metabolism in DD. Of course, we have not demonstrated recurrence of DD; merely recurrence of FFD. However, the cellular processes that contribute to 1 are likely to be influential in the other (certainly in terms of extracellular matrix turnover).

We have found strong evidence in a relatively small cohort of patients for a notable correlation between expression levels of genes involved in both collagen and proteoglycan turnover and early recurrence of FFD in the operated digit. This information might be useful in advising future patients both in terms of outcome prognosis and planning treatment, as well as having revealed enzymes that are potentially important in the pathogenesis of DD. Serum MMP levels have already been shown to correlate with tissue levels in patients with the condition.[9] To continue this work, therefore, we plan to assay preoperative serum and plasma levels of these proteinases and compare these with outcome in a subsequent cohort of DD patients.

REFERENCES

1. Thurston AJ. Dupuytren's disease. J Bone Joint Surg 2003;85B:469–477.
2. Rayan GM. Dupuytren disease: Anatomy, pathology, presentation, and treatment. J Bone Joint Surg 2007;89A:189–198.
3. Bulstrode NW, Bisson M, Jemec B, Pratt AL, McGrouther DA, Grobbelaar AO. A prospective randomised clinical trial of the intraoperative use of 5-fluorouracil on the outcome of Dupuytren's disease. J Hand Surg 2004;29B:18–21.
4. Dias JJ, Braybrooke J. Dupuytren's contracture: an audit of the outcomes of surgery. J Hand Surg 2006;31B:514–521.
5. Badalamente MA, Hurst LC. The biochemistry of Dupuytren's disease. Hand Clin 1999;15:35–42, v–vi.
6. Peterson JT. The importance of estimating the therapeutic index in the development of matrix metalloproteinase inhibitors. Cardiovasc Res 2006;69:677–687.
7. Hutchinson JW, Tierney GM, Parsons SL, Davis TR. Dupuytren's disease and frozen shoulder induced by treatment with a matrix metalloproteinase inhibitor. J Bone Joint Surg 1998;80B:907–908.
8. Johnston P, Chojnowski AJ, Davidson RK, Riley GP, Donell ST, Clark IM. A complete expression profile of matrix-degrading metalloproteinases in Dupuytren's disease. J Hand Surg 2007;32A:343–351.
9. Ulrich D, Hrynyschyn K, Pallua N. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in sera and tissue of patients with Dupuytren's disease. Plast Reconstr Surg 2003;112:1279–1286.
10. Bunker TD, Reilly J, Baird KS, Hamblen DL. Expression of growth factors, cytokines and matrix metalloproteinases in frozen shoulder. J Bone Joint Surg 2000;82B:768–773.
11. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29:602–608.
12. Chung KC, Pillsbury MS, Walters MR, Hayward RA. Reliability and validity testing of the Michigan Hand Outcomes Questionnaire. J Hand Surg 1998;23A:575–587.
13. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. J Burn Care Rehabil 1995;16:535–538.
14. Nuttall RK, Pennington CJ, Taplin J, Wheal A, Yong VW, Forsyth

PA, et al. Elevated membrane-type matrix metalloproteinases in gliomas revealed by profiling proteases and inhibitors in human cancer cells. Mol Cancer Res 2003;1:333–345.
15. Porter S, Scott SD, Sassoon EM, Williams MR, Jones JL, Girling AC, et al. Dysregulated expression of adamalysin-thrombospondin genes in human breast carcinoma. Clin Cancer Res 2004;10:2429–2440.
16. Beaton DE, Davis AM, Hudak P, McConnell S. The DASH outcome measure. What do we know about it now? Br J Hand Ther 2001;6:109–118.
17. Kevorkian L, Young DA, Darrah C, Donell ST, Shepstone L, Porter S, et al. Expression profiling of metalloproteinases and their inhibitors in cartilage. Arthritis Rheum 2004;50:131–141.
18. Davidson RK, Waters JG, Kevorkian L, Darrah C, Cooper A, Donell ST, Clark IM. Expression profiling of metalloproteinases and their inhibitors in synovium and cartilage. Arthritis Res Ther 2006;8:R124.
19. Jemec B, Grobbelaar AO, Wilson GD, Smith PJ, Sanders R, McGrouther DA. Is Dupuytren's disease caused by an imbalance between proliferation and cell death? J Hand Surg 1999;24B:511–514.
20. Jones GC, Corps AN, Pennington CJ, Clark IM, Edwards DR, Bradley MM, et al. Expression profiling of metalloproteinases and tissue inhibitors of metalloproteinases in normal and degenerate human Achilles tendon. Arthritis Rheum 2006;54:832–842.
21. Itoh Y. MT1-MMP: a key regulator of cell migration in tissue. IUBMB Life 2006;58:589–596.
22. Aimes RT, Quigley JP. Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. J Biol Chem 1995;270:5872–5876.
23. Colige A, Vandenberghe I, Thiry M, Lambert CA, Van Beeumen J, Li SW, et al. Cloning and characterization of ADAMTS-14, a novel ADAMTS displaying high homology with ADAMTS-2 and ADAMTS-3. J Biol Chem 2002;277:5756–5766.
24. Porter S, Clark IM, Kevorkian L, Edwards DR. The ADAMTS metalloproteinases. Biochem J 2005;386(Pt 1):15–27.
25. Kozma EM, Olczyk K, Wisowski G, Glowacki A, Bobinski R. Alterations in the extracellular matrix proteoglycan profile in Dupuytren's contracture affect the palmar fascia. J Biochem 2005;137:463–476.