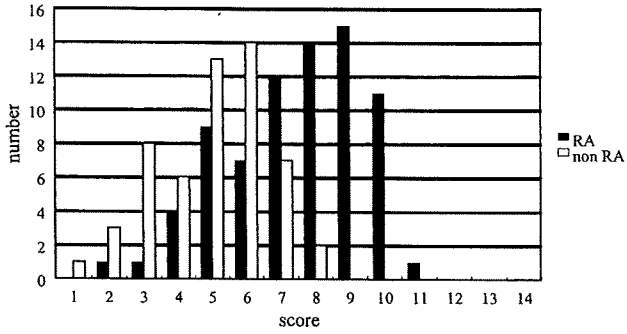

Figure 1. Scoring of 129 patients with undifferentiated arthritis by the Leiden Early Arthritis Cohort prediction rule; 75 had progressed to rheumatoid arthritis (RA) at 1 year. The distribution of the scores at baseline is shown, calculated according to the Leiden Early Arthritis Cohort prediction rule. Scores were rounded to the nearest number encoding in 0.5 or 0.0 (i.e., scores ≤0.5 are in category 0, scores >0.5 to 1.5 are in category 1, etc.), as described previously (3). RA = progression to RA group (n = 75); non RA = no progression to RA group (n = 54).

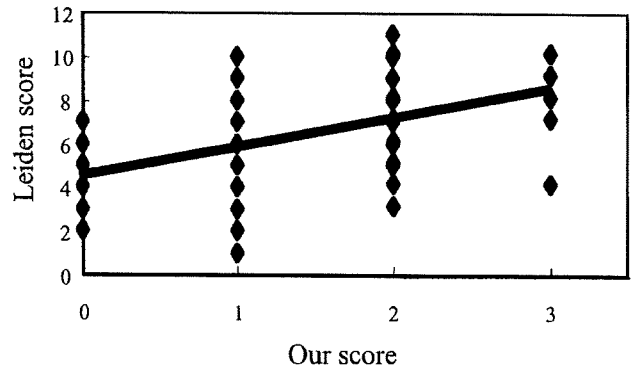

Figure 2. A positive correlation between the Leiden Early Arthritis Cohort prediction score and our prediction score. The statistical association was calculated by Spearman's rank correlation and a strong correlation was found between the 2 scores (R = 0.635, $P < 0.0001$).

treated with glucocorticoids, whereas 10 patients (18.5%) received glucocorticoids among 54 patients with UA that did not progress to RA ($P < 0.0001$). The diagnoses of 54 patients with UA that did not progress to RA at 1 year include Sjögren's syndrome (n = 11), osteoarthritis (n = 9), chronic hepatitis (n = 6), scleroderma (n = 3), palindromic rheumatism (n = 3), systemic lupus erythematosus (n = 2), fibromyalgia syndrome (n = 2), adult-onset Still's disease (n = 1), myofasciitis of unknown etiology (n = 1), polymyalgia rheumatica (n = 1), remitting seronegative symmetrical synovitis with pitting edema (n = 1), pseudogout (n = 1), and UA (n = 13). The Leiden Early Arthritis Cohort prediction scores were also calculated. Figure 1 shows the distribution of prediction scores, with a mean high score in patients with UA that progressed to RA of 8 versus 5 in patients with UA that did not progress to RA ($P < 0.0001$). According to cutoff levels of ≤6 and ≥8 in the Leiden Early Arthritis Cohort prediction rule, the NPV and PPV were 67.2% and 95.3%, respectively, in the present study population.

Evaluation of the prediction rule by serologic variables and MRI in comparison with the Leiden Early Arthritis Cohort prediction score. We evaluated the prediction rule by serologic variables and MRI in patients with UA, according to our previous report (6–8) as described above. The statistics demonstrate that the PPV was 79.7%, the NPV was 63.0%, the specificity was 75.9%, the sensitivity was 68.0%, and the accuracy was 71.3%. With respect to UA patients whose Leiden Early Arthritis Cohort prediction score was ≥8 (n = 43; PPV of 95.3% among the 41 of these 43 patients who progressed to RA by the Leiden Early Arthritis Cohort prediction score), our prediction rule was able to classify the progression to RA equally well (38 [88.4%] of 43 patients, not significantly different versus the Leiden Early Arthritis Cohort prediction score). In addition, with respect to UA patients whose Leiden Early Arthritis Cohort prediction score was ≤6 (n = 67; NPV of 67.2% among the 45 patients who did not progress to RA by the Leiden Early Arthritis Cohort prediction score), the present prediction rule predicted that 52 of 67 patients would not progress to RA (77.6%; not significantly equal to the Leiden Early Arthritis Cohort prediction rule). Fifteen of 67 patients whose Leiden Early Arthritis Cohort prediction score was ≤6 at baseline were classified as having RA by our score, and in fact, 7 patients progressed to RA at 1 year (PPV in this population is 46.7%). Accordingly, a positive correlation between the Leiden Early Arthritis Cohort prediction score and our score was clearly determined (R = 0.635, $P < 0.0001$) (Figure 2). Furthermore, the 3 critical objective characteristics were preferentially found among UA patients whose Leiden Early Arthritis Cohort prediction score was ≥8 as compared with those whose score was ≤6 (Table 2). Anti-CCP antibodies and MRI-proven bone edema were the most specifically distributed in UA patients with a score of ≥8 (Table 2).

Table 2. Distribution of MRI-proven symmetric synovitis, MRI-proven bone edema, anti-CCP antibodies, and IgM-RF in 129 patients with UA according to the Leiden Early Arthritis Cohort prediction score*

	Leiden Early Arthritis score		
	Score ≤6 (n = 67)	Score ≥8 (n = 43)	*P*
Symmetric synovitis	44.8	81.4	0.0001
Bone edema	10.4	48.8	< 0.0001
Bone erosion	13.4	30.2	0.032
Anti-CCP antibodies	6.0	86.0	< 0.0001
IgM-RF	26.9	67.4	< 0.0001
CRP level	38.8	69.8	0.0015
MMP-3	16.4	37.2	0.013
Progression to RA	32.8	95.3	< 0.0001

* Values are the percentage. Compared with patients with undifferentiated arthritis (UA) who scored ≤6, MRI-proven symmetric synovitis, MRI-proven bone edema, anti-CCP antibodies, and IgM-RF were densely distributed in the UA patients who scored ≥8. See Table 1 for definitions.

Table 3. Qualification of each variable at baseline for the prediction of progression to rheumatoid arthritis from undifferentiated arthritis*

	Sensitivity, %	Specificity, %	OR	*P*	95% CI	PPV, %	NPV, %	LR positive	LR negative	Accuracy, %
Serologic variables										
IgM-RF	52.0	70.4	2.57	< 0.05	1.53–4.34	70.9	51.4	1.76	0.682	59.7
Anti-CCP antibodies	57.3	92.6	16.8†	< 0.0001†	7.63–36.99	91.5†	61.0	7.74	0.461	72.1
MMP-3	36.0	85.2	3.23	< 0.01	1.73–6.03	77.1	48.9	2.43	0.751	56.6
MRI findings										
Symmetric synovitis	74.7	59.3	4.07	< 0.005	2.52–7.30	71.8	62.7	1.84	0.427	68.2
Bone edema	41.3	90.7	6.90†	< 0.0001†	3.34–14.29	86.1†	52.7	4.44	0.647	62.0
Bone erosion	29.3	90.7	4.07	< 0.0001	1.94–8.52	81.5	48.0	3.18	0.779	55.0

* OR = odds ratio; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; see Table 1 for additional definitions.
† Most significant in serologic variables or MRI findings.

Procedure for the improvement of PPV for the prediction of RA development by our objective measures. The present data showed a 79.7% PPV for the prediction of RA development using our objective measures, which is not sufficient evidence to recommend that physicians start administering DMARDs if the patients do not yet fulfill the established classification criteria. According to *P* values and odds ratios of independent predictive variables for the development of RA, anti-CCP antibodies as a serologic variable and bone edema on MRI were found to be the most specific (Table 3). Therefore, if UA patients tested positive for anti-CCP antibodies and showed MRI-proven bone edema, they will progress to RA within 1 year; the PPV in such cases was 100% (Table 4). In the case of the score in Table 4, we examined MRI-proven bone edema of the symptomatic hand instead of both hands. As shown in Table 4, the PPV in such cases was still 100%, whereas the sensitivity of detection was low as compared with both hands (16 patients by the symptomatic hand versus 22 patients by both hands, 27.3% reduction by the symptomatic hand).

DISCUSSION

In clinical practice, patients presenting with early arthritis frequently have an undifferentiated disease that may progress to polyarthritis by fulfilling the ACR criteria for RA, or they may have a more benign disease course. The ACR criteria have been criticized for their low discriminative ability in patients presenting with recent-onset arthritis (14–16). Therefore, a new set of criteria that applies to early UA and that identifies patients with UA who will progress to RA is needed, since a recent study strongly suggests that treatment is effective in the early phase of arthritis, before the disease is established (4).

To our knowledge, the present study is the first validation report of Japanese patients with UA using the Leiden Early Arthritis Cohort prediction rule. The Leiden Early Arthritis Cohort prediction rule is clinically useful, especially to identify patients who will progress to RA, i.e., those whose prediction score is ≥8. However, a difference was found in the low NPV of the Leiden score in our study population as compared with the original report (91% NPV in the original report from The Netherlands) (3). This could be due to the fact that the present study population may have included more RA patients with low disease activity whose disease developed from UA compared with the original study population in The Netherlands. In addition, the rate of progression to RA in this cohort is high as compared with previous observations, including the Leiden Early Arthritis Cohort (3,17). The Leiden Early Arthritis Cohort has identified that the presence of arthritis

Table 4. An achievement of 100% PPV for the development of RA from UA by a combination of anti-CCP antibodies and MRI-proven bone edema*

No. patients	Variables at baseline: Anti-CCP antibodies	Variables at baseline: Bone edema by both hands	Variables at baseline: Bone edema by the symptomatic hand	RA progression (n = 75)	No RA progression (n = 54)
22	Positive	Positive		22 (100)	0 (0.0)
25	Positive	Negative		21 (84.0)	4 (16.0)
14	Negative	Positive		9 (64.3)	5 (35.7)
68	Negative	Negative		23 (33.8)	45 (66.2)
16	Positive		Positive	16 (100)	0 (0.0)
31	Positive		Negative	27 (87.1)	4 (12.9)
10	Negative		Positive	5 (50.0)	5 (50.0)
72	Negative		Negative	27 (37.5)	45 (62.5)

* Values are the number (percentage). PPV = positive predictive value; RA = rheumatoid arthritis; UA = undifferentiated arthritis; anti-CCP = anti–cyclic citrullinated peptide; MRI = magnetic resonance imaging.

in the wrists and finger joints, as well as in the upper extremities at study entry, is an advantage in the progression of RA (3). All of the subjects in the present study expressed rheumatic manifestations of the wrists and finger joints; therefore, they could already be selected as being biased to the progression of RA. This discrepancy may cause a difference in the prediction efficacy of the Leiden Early Arthritis Cohort prediction rule toward the 2 cohort populations. A prospective clinical analysis of the present study population, including a radiographic joint damage study, is necessary to answer this question.

There is a significant difference between our score and that established by the Leiden Early Arthritis Cohort, with respect to not only the prediction rule but also to the selection of the variables. The Leiden Early Arthritis Cohort adopted a cutoff value of ≥8 for the PPV and ≤6 for the NPV for the prediction, whereas our score can draw a threshold of only one line of prediction. The Leiden Early Arthritis Cohort variables stress clinical manifestations; however, our scoring system gives weight only to serologic autoantibodies and early joint damage as verified by MRI. The NPV of the 2 prediction rules was similar (63.0% versus 67.2%), although the PPV was superior in the Leiden score (79.7% versus 95.3%). Nevertheless, our prediction rule identified 52 patients of 65 predicted upon admission, whereas the Leiden score identified only 41 patients of 43 predicted. In an attempt to improve the PPV, we demonstrated that the combination of anti-CCP antibodies with bone edema gave a 100% PPV in 22 patients (Table 4). Considering the significant correlation between the 2 rules, our prediction rule is considered to be equally valuable to predict the development of RA in patients with UA.

The ESCISIT states that clinical examination is still the gold standard in detecting synovial inflammation; however, the expert committee is aware of the importance of MRI in greater sensitivity for detection (4). In the case of the patients who progressed to RA that were identified by our prediction rule rather than by the Leiden score, MRI helped identify patients with UA who were not able to be identified by clinical manifestation. The result that our rule can predict the progression of RA whose Leiden Early Arthritis Cohort prediction score was ≤6 at baseline may reflect this notion. Our present data give clear evidence of MRI that is sensitive as well as clinically valuable for patients with early arthritis. Based on a combination of serologic anti-CCP antibodies, we suggest that a UA patient whose score is ≥2 should receive DMARDs early, especially if they both show MRI-proven bone edema and are anti-CCP positive. We also tried to simplify the method by using MRI of the symptomatic hand instead of both hands, in the case of seeking MRI-proven bone edema. In this case, detection sensitivity decreased by 27.3%, whereas the PPV was still 100%. This would show practical advantages for clinical use if a single-hand MRI is as good as both hands; however, additional studies by other groups are necessary.

It remains to be determined whether the present rule is also effective in predicting radiographic joint destruction. It is likely to be effective, since bone change in MRI as well as serologic autoantibodies are predictors for subsequent radiographic progression (10,11,16,17). The present prediction rule revealed that patients with early-stage RA with both MRI-proven bone edema and anti-CCP antibodies upon admission progressed with a high frequency to erosive disease (Tamai M et al: unpublished observations). However, a prospective analysis of the present study remains to be carried out in order to precisely answer these questions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Eguchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tamai, Kawakami, Uetani, Aoyagi, Eguchi.

Acquisition of data. Tamai, Kawakami, Uetani, Takao, Arima, Iwamoto, Fujikawa, Aramaki, Kawashiri, Ichinose, Kamachi, Nakamura, Origuchi, Ida, Eguchi.

Analysis and interpretation of data. Tamai, Kawakami, Aoyagi.

REFERENCES

1. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
2. Van der Helm-van Mil AH, Huizinga TW. Diagnostic and therapeutic opportunities in undifferentiated arthritis. Int J Adv Rheumatol 2007;5:34–9.
3. Van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum 2007;56:433–40.
4. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34–45.
5. McQueen FM. Magnetic resonance imaging in early inflammatory arthritis: what is its role? Rheumatology (Oxford) 2000;39:700–6.
6. Tamai M, Kawakami A, Uetani M, Takao S, Rashid H, Tanaka F, et al. Early prediction of rheumatoid arthritis by serological variables and magnetic resonance imaging of the wrists and finger joints: results from prospective clinical examination [letter]. Ann Rheum Dis 2006;65:134–5.
7. Tamai M, Kawakami A, Uetani M, Takao S, Tanaka F, Nakamura H, et al. The presence of anti–cyclic citrullinated peptide antibody is associated with magnetic resonance imaging detection of bone marrow oedema in early stage rheumatoid arthritis [letter]. Ann Rheum Dis 2006;65:133–4.
8. Tamai M, Kawakami A, Uetani M, Takao S, Tanaka F, Fujikawa K, et al. Bone edema determined by magnetic resonance imaging reflects severe disease status in patients with early-stage rheumatoid arthritis. J Rheumatol 2007;34: 2154–7.
9. Shinozaki M, Inoue E, Nakajima A, Hara M, Tomatsu T, Kamatani N, et al. Elevation of serum matrix metalloproteinase-3 as a predictive marker for the long-term disability of rheumatoid arthritis patients in a prospective observational cohort IORRA. Mod Rheumatol 2007;17:403–8.
10. Lassere M, McQueen F, Ostergaard M, Conaghan P, Shnier R, Peterfy C, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exercise 3: an international multicenter reliability study using the RA-MRI Score. J Rheumatol 2003;30:1366–75.
11. Conaghan P, Lassere M, Ostergaard M, Peterfy C, McQueen F,

O'Connor P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Exercise 4: an international multicenter longitudinal study using the RA-MRI Score. J Rheumatol 2003;30:1376–9.
12. McQueen FM, Benton N, Perry D, Crabbe J, Robinson E, Yeoman S, et al. Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. Arthritis Rheum 2003; 48:1814–27.
13. Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum 2003;48:64–71.
14. Harrison BJ, Symmons DP, Barrett EM, Silman AJ, and the American Rheumatism Association. The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. J Rheumatol 1998;25:2324–30.
15. Harrison B, Symmons D. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcome at three years. Rheumatology (Oxford) 2000;39:939–49.
16. Symmons DP, Hazes JM, Silman AJ. Cases of early inflammatory polyarthritis should not be classified as having rheumatoid arthritis. J Rheumatol 2003;30:902–4.
17. Van der Helm-van Mil AH, Detert J, le Cessie S, Filer A, Bastian H, Burmester GR, et al. Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making. Arthritis Rheum 2008;58:2241–7.

M. FUJIOKA
Chief of the Department of Plastic and Reconstructive Surgery, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan.

Artificial dermis: A new material for wound treatment

Introduction

Wound bed preparation allows uncomplicated wounds to heal quickly without surgery.[1] However, the treatment of tendon- or bone-exposed wounds with skin defects or complex, chronic ulcers remains challenging.[2] Formerly, resurfacing these wounds required some vasucularized flaps, because a free skin graft would not take on unfavorable wound beds, such as in the presence of infected granulation and poorly vascularized tissues.

Studies involving various temporary biological dressing materials employed to cover and protect the wound surface have been reported.[3-5] While most of these biological or synthetic dressing materials minimize fluid loss from the wound, prevent wound infection, reduce pain, and thus support wound healing, they do not positively promote wound healing.

Artificial dermis, which is composed of atelocollagen sponge and a silicone membrane, is beneficial for these wounds because of its unique characteristics. Atelocollagen sponge allows the early infiltration of mononuclear cells and fibroblasts, leading to the rapid resolution of inflammatory reactions and better growth of granulation tissue. Morever, the silicone membrane protects against the loss of fluid, protein, and electrolytes, which helps maintain a suitable environment for wound healing.[6-7] Such a collagen membrane preparation has been manufactured with the aim of enhancing wound healing following periodontal surgery.

In this article, I will introduce the benefits of artificial dermis, presenting several cases.

Material structure and utility of artificial dermis

The artificial dermis is composed of two layers: a lower layer of atelocollagen, and an upper layer comprising a silicone sheet. The atelocollagen is purified from bovine dermis (Terudermis®, Orimpas-Terumo Co., Ltd., Tokyo, Japan. Integra®, Integra Life Science Co., Ltd., NJ, USA) or porcine tendon (Pelnac®, Gunze Co., Ltd., Kyoto, Japan) collagen, neutralized and freeze-dried to produce sponge membranes *(Figure 1)*. After debridement, the artificial dermis is applied to wounds, and ointment-impregnated gauze is applied to prevent wound drying. The adapted atelocollagen sponge promotes the early infiltration of mononuclear cells and fibroblasts and better growth of connective tissue strands and epithelium. Consequently, abundant granulation tissue develops on the wound surface, over which free skin grafting can be performed after about two weeks *(Figure 2)*.[8-9]

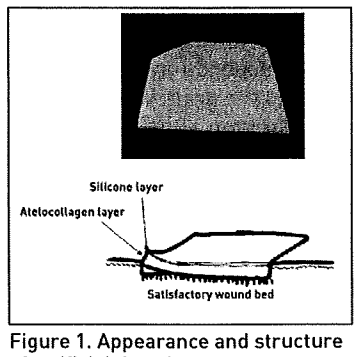

Figure 1. Appearance and structure of artificial dermis.

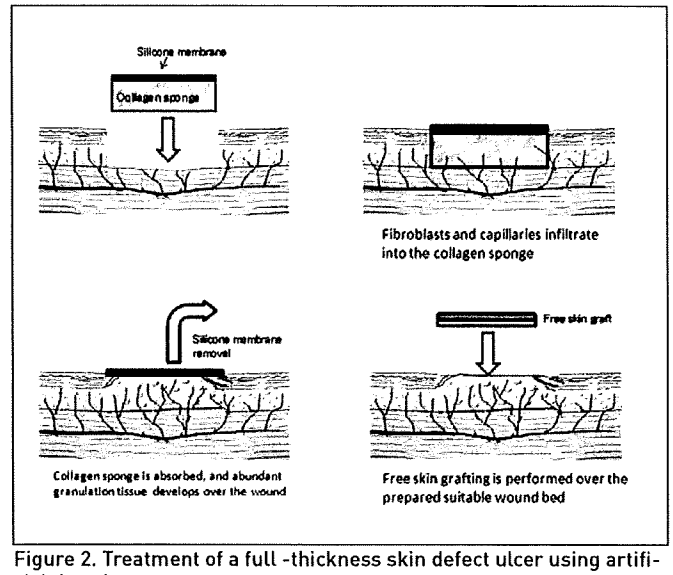

Figure 2. Treatment of a full -thickness skin defect ulcer using artificial dermis.

Experimental outcomes

To evaluate the beneficial effect of artificial dermis implantation over the wound, an animal study using rabbits was performed. Fifty young rabbits underwent palatal mucoperiosteal denudation at two sites, each being 4 mm in diameter, and artificial dermis was placed over the left palatal bone; the right defect was untreated as a control *(Figure 3)*. On sacrifice three days after the operation, the artificial dermis-implanted side showed the early infiltration of mononuclear and spindle cells into the applied matrix, and the control side showed a wound covered with a single-layer blood clot with

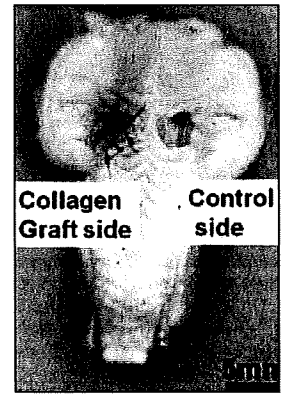

Figure 3. Surgical procedure. Two 4 mm-diameter pieces of mucoperiosteum were removed bilaterally from the hard palate. On the left side, the atelocollagen matrix sheet (arrowhead) was implanted directly over the denuded bone and sutured. The opposite side was left open (control).

neutrophilic leukocytes and exudates *(Figure 4)*. On sacrifice after ten days, the atelocollagen implanted side showed that the surface was already covered with epithelium, and the regenerating connective tissue was composed of collagen bundles that extended in the same direction and were clearly oriented, whereas the collagen bundles on the control side extended in various directions *(Figure 5)*.

Rabbits were then sacrificed 20 weeks after the operation, and the area of palatal scarring was measured to examine wound contraction *(Figure 6)*. There was a significant difference in the areas of palatal scarring between the atelocollagen-implanted and control sides. The areas of scarring on the atelocollagen-implanted side were an average of 11.1% larger than those on the control side, which means that wound contraction and scarring contracture can reduced by adapting artificial dermis. Histologically, the structure of the degenerated tissue on the atelocollagen-implanted side showed that the formation of rete ridges and elongated dermal papillate processes, being similar to the normal mucosa.[6]

Early resurfacing and the nomal stracture of regenerated tissue are the reasons for the reduced contraction of scars.[10-11]

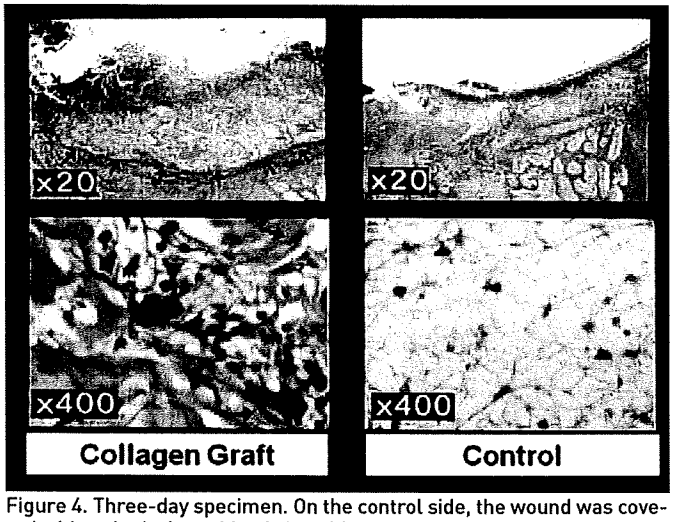

Figure 4. Three-day specimen. On the control side, the wound was covered with a single-layer blood clot with neutrophilic leukocytes and exudates. The infiltration of mononuclear and spindle cells (arrow) into the applied matrix was observed on the atelocollagen-implanted side.

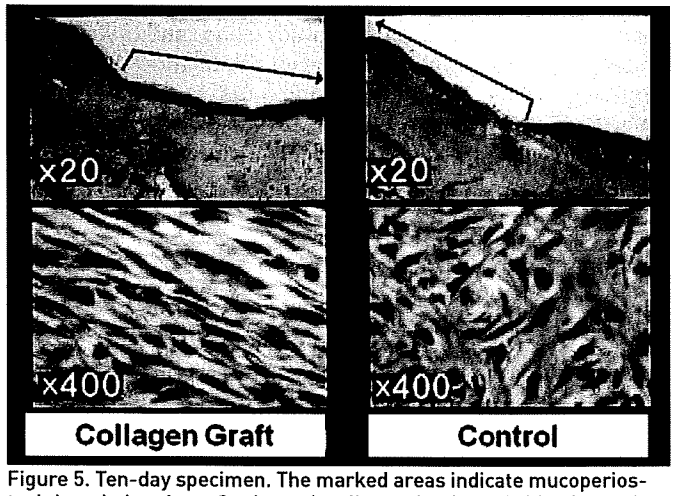

Figure 5. Ten-day specimen. The marked areas indicate mucoperiosteal denuded regions. On the atelocollagen-implanted side, the surface was covered with epithelium, and the regenerating connective tissues were composed of collagen bundles which extended in the same direction and were more clearly oriented than those on the control side.

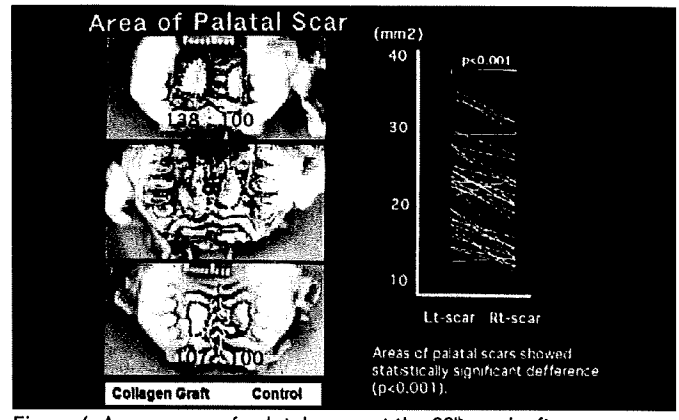

Figure 6. Appearance of palatal scars at the 20th week after surgery (left). Each scarred area on the atelocollagen-implanted side was larger than on the control side. Analysis of maxillary scar measurement data (right). Significant differences were detected between the groups regarding the scar area by the paired t-test ($p<0.001$).

Clinical application of artificial dermis

COVERING OF PERIODONTAL AND ORAL MUCOSAL DEFECTS

Dentists and odontologists are familiar with artificial dermis because they use it in the treatment of periodontal mucosal defects for root coverage.[12-13] Plastic surgeons have also utilized artificial dermis to cover denuded bone surfaces following cleft palate repair in order to resurface the wound quickly. Atelocollagen sponge is known to reduce the surgical interference with maxillary bone growth.[6] Figures 7 show intraoperative photographs of cleft palate repair *(Figure 7-1)*. Atelocollagen matrix was applied onto the mucoperiosteal denuded hard palate caused by the push back procedure. These exposed-bone surfaces were resurfaced within one week without free skin graft application, and showed no scar contraction one year later *(Figure 7-2)*.

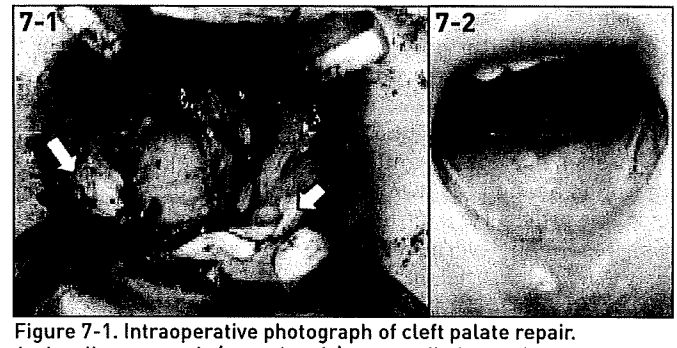

Figure 7-1. Intraoperative photograph of cleft palate repair. Atelocollagen matrix (arrowheads) was applied over the mucoperiosteal denuded hard palate caused by the push back procedure.
Figure 7-2. These bone-exposed wounds were resurfaced without a free skin graft and showed no scar contraction 1 year later.

COVERING OF TENDON- OR BONE-EXPOSED WOUNDS

Skin grafts can survive because oxygen and nutrients diffuse into them from the underlying wound bed. Their long-term survival depends on a new blood supply route forming from the wound to the graft. When the wound bed does not receive sufficient oxygen supply, the skin graft fails.[14] For this reason, grafted skin cannot survive on poorly vascularized tissue such as bone and tendon surfaces. So, resurfacing bone-exposed wounds has required pedicle or free flaps showing high-level morbidity at the donor site, being skill- and time-intensive. In particular, the emergent treatment of an injury with Gustilo-Anderson III B or C type open fracture is very labor-intensive for surgeons. The unique characteristic of artificial dermis, promoting granular regeneration even on bare bone, can reduce →

→ the severity of Gustilo-Anderson III B or C to Gustilo-Anderson III A or II fractures, which may allow the resurfacing with a free skin graft instead of flap surgery.

Case 1. Bone-exposed wound with large skin defect (Gustilo-Anderson III B open fracture)

A 7-year-old girl sustained a detrition injury to the left leg due to being run over by a car, and was brought to our medical center. The patient had a left leg skin defect measuring 30 x 10 cm, and a 5 x 3 cm bone-exposed area was observed *(Figure 8-1)*. An X-ray revealed fracture and bone defect of the fibula *(Figure 8-2)*. Emergent surgery including wound cleansing, debridement, and application of an artificial dermis over the entire wound was performed *(Figure 8-3)*. Fourteen days after surgery, abundant granulation tissue had developed on the wound surface including over the bone and tendon, and so the patient could undergo free skin grafting. The wound was completely resurfaced by two weeks after skin grafting, and has been maintained without relapse, ankle joint contraction, or hypertrophic scar formation for one year *(Figure 8-4)*.

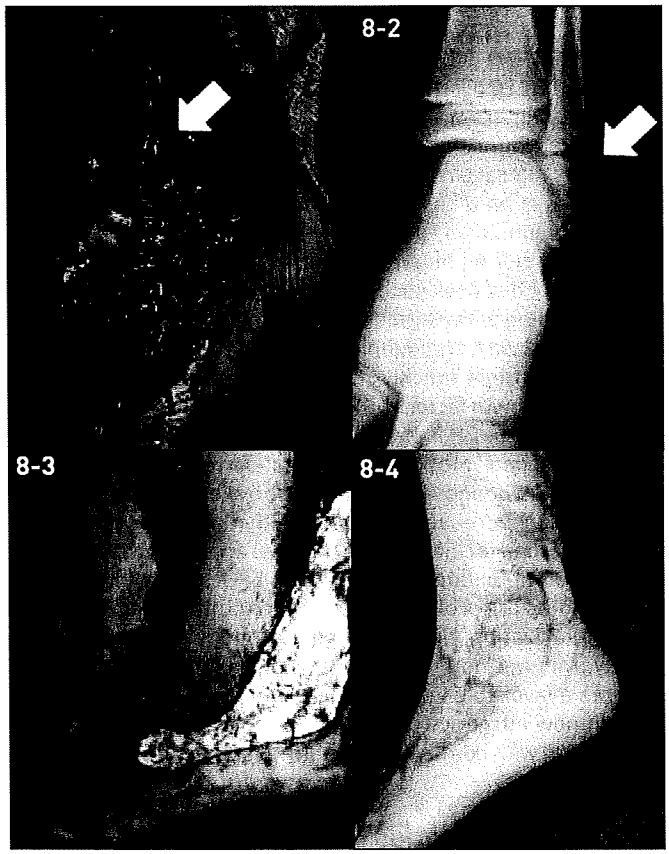

Figure 8-1. Case 1. The patient had a left ankle skin defect measuring 30 x 10 cm, and a 5 x 3 cm bone-exposed area was observed (arrow). Figure 8-2. An X-ray revealed fracture and bone defect of the fibula (arrow). Figure 8-3. Application of artificial dermis over the entire wound was performed. Figure 8-4. One year after surgery. The wound had been completely resurfaced and maintained without relapse, ankle joint contraction, and hypertrophic scar formation.

Case 2. Bone-exposed wound with a large skin defect (deep burn)

A 63-year-old man sustained deep dermal burns to the left leg, comprising 5% of the total body surface area, due to his trousers catching fire *(Figure 9-1)*. Initial surgery was carried out the next day to remove all necrotic tissue. Intraoperative examination showed that soft tissue over the tibia had degenerated, so that the tibia was exposed after debridement *(Figure 9-2)*. A mesh skin graft was performed over this residual soft tissue, and artificial dermis was applied onto the bone surface *(Figure 9-3)*. Three weeks after the initial surgery, the exposed bone was almost covered with granulation tissue. The patient underwent free skin grafting over it, and the wound was completely resurfaced one month after the second surgery *(Figure 9-4)*.

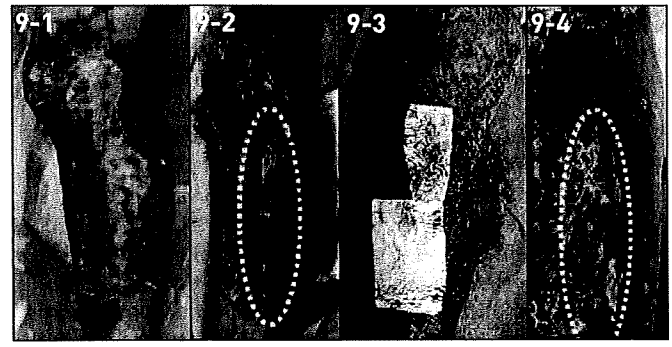

Figure 9-1. Case 2. A full-thickness leg burn comprising 5% of the total body surface area was observed. Figure 9-2. After debridement, the tibia was exposed (dotted circle). Figure 9-3. A mesh skin graft was applied over this residual soft tissue, and artificial dermis was applied over the bone surface. Figure 9-4. Three weeks after surgery, the exposed bone was almost covered with granulation tissue (dotted circle).

Case 3. Tendon-exposed wound with a large skin defect

A 39-year-old man sustained a detrition injury to the left leg due to being run over by a truck. The patient showed an extensive soft tissue defect. The initial treatment carried out by orthopedic surgeons was to control bleeding, debridement, and to perform wet to dry dressing. The patient was then referred to our department to resurface the wound two weeks later. At our first examination, the left leg showed 30 x10 cm skin defect, and a 10 x 10 cm Achilles tendon-exposure area was observed *(Figure 10-1)*.

Angiography showed that the posterior tibial and peroneal arterial flow was interrupted, and the foot was vascularized only by the anterior tibial flow. It was difficult to cover the wound using a free flap transfer, because the blood flow to both the foot and recipient vessels were unstable. Thus, treatment was planned as a two-stage approach; the first stage being surgery where a mesh skin graft was applied to cover the whole wound, and artificial dermis was applied over

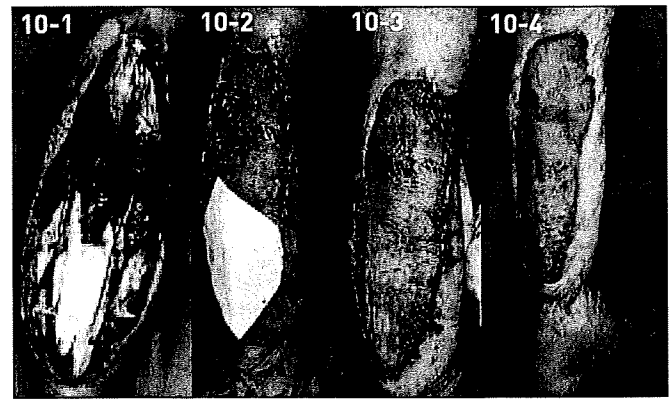

Figure 10-1. First examination of case 3. A large Achilles tendon-exposed area was observed.
Figure 10-2. The patient underwent free skin grafting, and artificial dermis was applied over the grafted skin where the tendon was exposed.
Figure 10-3. Four weeks after surgery, all of the applied free skin graft successfully took.
Figure 10-4. The patient could walk without a cane 1 month after surgery.

the grafted skin where the tendon was exposed *(Figure 10-2)*. If the skin graft on the tendon did not take, abundant granulation tissue development on the tendon would be expected as an effect of the atelocollagen sponge. Furthermore, more than half of the wound should be resurfaced over the muscle region, which might improve the patient's wound state and general condition. However, the entire skin graft completely took fourteen days after surgery, beyond any expectation *(Figure 10-3)*. The patient did not require additional surgery, and could walk without a cane one month after surgery *(Figure 10-4)*.

RESURFACING OF SMALL WOUNDS AS A TEMPORARY OR PERMANENT SKIN SUBSTITUTE

Biological dressings used for the temporary coverage of open wounds exert both mechanical and physiological effects by protecting the wound, maintaining microbial control. [3-5,15] Wang et al. reported that artificial dermis protected the wound significantly longer than Biobrane®, and prevents contraction.[16] Artificial dermis can protect the wound long enough to promote wound healing, or prevent the open wound from resurfacing immediately until the secondary surgery can be preformed.[16] This simple method is useful, especially for the elderly, to treat full-thickness scalp defects.[17]

Case 4. Mucosa skin defect (dog bite to the lip)

A 5-year-old boy sustained a full-thickness skin mucosa defect of the upper lip due to a dog bite. The soft tissue defect measured 1.7 x 1.0 cm (Figure 11-1). Emergent treatment including wound cleansing and artificial dermis application over the wound *(Figure 11-2)*. The wound was resurfaced within three weeks without skin grafting. Six months after the surgery, less marked scarring remained on the upper lip showing an acceptable appearance without a hypertrophic scar or severe deformity of the lip *(Figure 11-3)*.

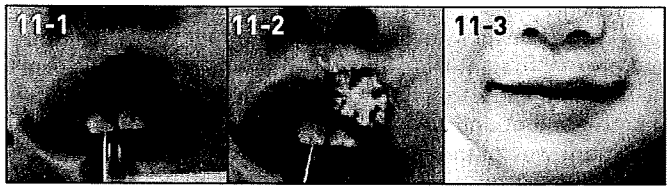

Figure 11-1. Case 4. A full-thickness skin mucosa defect of the upper lip due to a dog bite was observed.
Figure 11-2. Artificial dermis was applied over the wound.
Figure 11-3. Six months after the injury, an acceptable appearance without hypertrophic scar formation or severe lip deformity was maintained without skin grafting.

Case 5. Possible squamous cell carcinoma (Figure 12)

A 74-year-old man consulted our medical center complaining of a 2-year history of a chronic ulcer. The patient had sustained deep dermal burns to the left leg and undergone a free skin graft 14 years previously. On examination, an ulcer measuring 1.7 x 1.0 cm was found on the posterior side of the knee, where burn scar contraction had occurred *(Figure 12)*. Excision biopsy was performed; aware of possible squamous cell carcinoma (SCC), and the full-thickness skin defect was covered with artificial dermis. Histological analysis of the biopsy led to a diagnosis one week later of a benign skin condition, and so a second surgery including the release of scar contraction and free skin grafting was performed. If the histological report had revealed malignant neoplasm, radical abrasion around the ulcer and resurfacing with some large local or free flap would have been required.

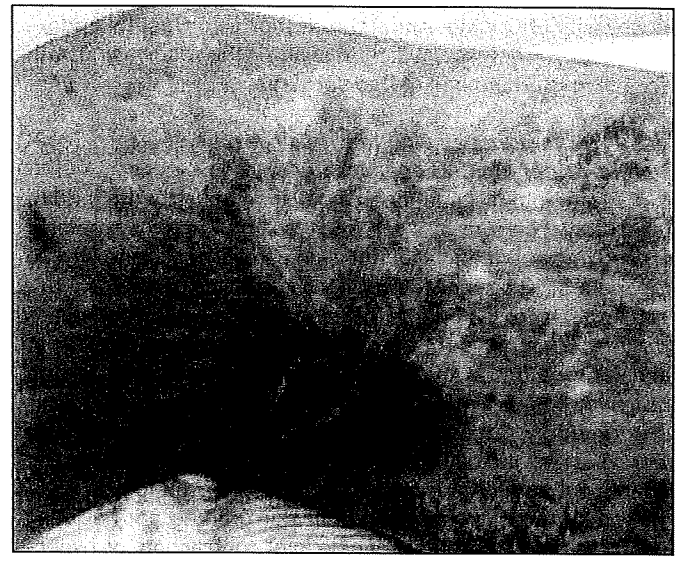

Figure 12. First examination of case 5. A chronic ulcer developed on a burn scar, believed to be SCC.

Combination treatment with basic fibroblast growth factor (bFGF) and artificial dermis to improve complex wounds

Chronic wounds seldom result from a single factor; several factors interact in the formation of chronic wounds.[18] Common causes of hard-to-heal chronic ulcers are previous radiation to the wound area, diabetes mellitus, and certain infections. Problems in wound healing frequently occur in patients who have systemic diseases such as collagen diseases, because they must be treated with steroids, which delay wound healing.[19]

Treatment with angiogenic cytokines allows these chronic ulcers to heal more quickly.[7,20-22] To prepare a favorable wound bed, several growth factors have been applied clinically. Of these growth factors, bFGF is the only angiogenic cytokine currently available in Japan.[7] Marks reported that dermal wounds treated with collagen sponges seeded with fibroblasts or coated with bFGF show an increased level of reepithelialization, indicating that this method facilitates early dermal and epidermal wound healing.[22] Combination treatment with bFGF and artificial dermis promotes the proliferation and recruitment of fibroblasts, neovascularization, and synthesis of collagen fibers. Consequently, this method improves complex wounds and rapidly prepares a favorable wound bed.

I will now introduce the outcomes of chronic ulcers which were treated with combination treatment comprising bFGF and artificial dermis.

Patients and Methods

The artificial dermis was cut to create multiple slits, like a mesh skin graft, through which exudates could be drained and sprayed bFGF could reach the atelocollagen sponge. After debridement, the slit artificial dermis was applied to the wounds, and bFGF (Trafermin, Fiblast Spray®, Kaken Pharmaceutical Co., Ltd., Tokyo, Japan) was sprayed. Ointment-impregnated gauze was applied to wounds. Treatment with bFGF continued until patients underwent secondary skin grafting *(Figure 13)*.

Case 6. Complex chronic ulcer

A 30-year-old woman with systemic lupus erythematosis (SLE) and, who had been treated with 20 mg/day of prednisolone for 10 years, and had had a leg ulcer for two years. Cleansing and

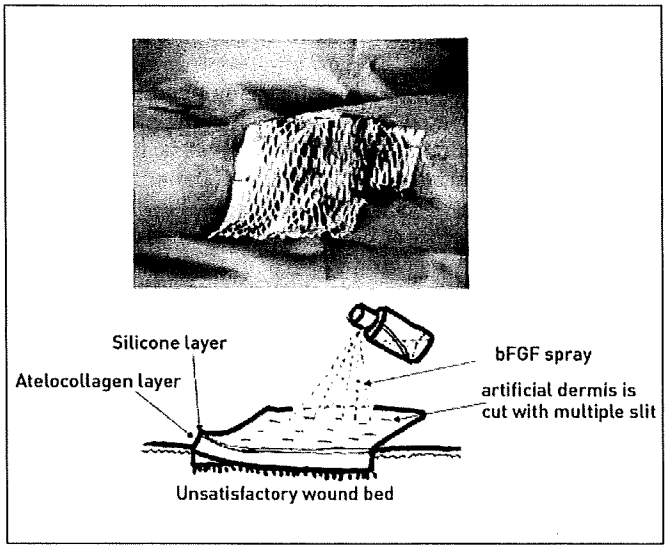

Figure 13. Meshed artificial dermis application (upper) and schema of combination treatment with basic fibroblast growth factor and artificial dermis for the treatment of complex wounds (lower).

wet-to-dry dressing was continued for two weeks. However, a favorable wound bed did not develop *(Figure 14-1)*. Debridement was performed again, and a meshed artificial dermis was applied, after which bFGF was sprayed every day, and the wound began to be cleaned two weeks later. After three weeks, abundant granulation tissue had developed on the wound surface *(Figure 14-2)*. The patient underwent free skin grafting. The wound was fully resurfaced at two weeks after skin grafting, and has been maintained without relapse for two years *(Figure 14-3)*.

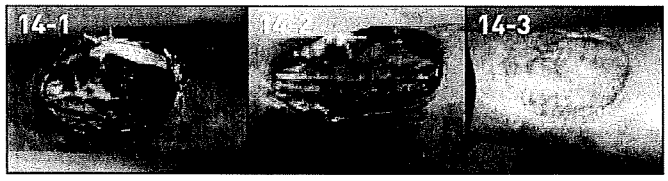

Figure 14-1. First examination of case 6. Complex chronic ulcer due to systemic lupus erythematosis and the long-term administration of prednisolone had been present on the leg for two years. Application of usual wound bed preparation method had not improved the wound condition.
Figure 14-2. Three weeks after the combination treatment with basic fibroblast growth factor and artificial dermis. Abundant granulation tissue suitable for free skin grafting was observed.
Figure 14-3. The wound was completely resurfaced favorably after skin grafting, and has been maintained without relapse for two years.

Case 7. Tendon-exposed deep burn (heat-press injury)

A 43-year-old woman sustained a heat-press injury to the right middle and ring fingers due to being caught in a hot iron press *(Figure 15-1)*. Debridement was carried out the next day. Intraoperative examination showed that palmer soft tissue including the skin, superficial flexor tendon, digital vessels, and nerves on the radial side of the middle finger had been damaged. After the debridement of all necrotic tissue, the exposed deep flexor tendon was covered with artificial dermis *(Figure 15-2)*. bFGF was sprayed every day, and the tendon was almost covered with fresh granulation tissue two weeks later *(Figure 15-3)*. After three weeks, abundant granulation tissue had developed on the exposed flexor tendon surface, and so the patient underwent nerve grafting and free skin grafting *(Figure 15-4)*. The wound was completely resurfaced by two weeks after skin grafting *(Figure 15-5)*. Flexor function and normal sensation of the ring and middle fingers were restored after tenolysis surgery (Figure 15-6).

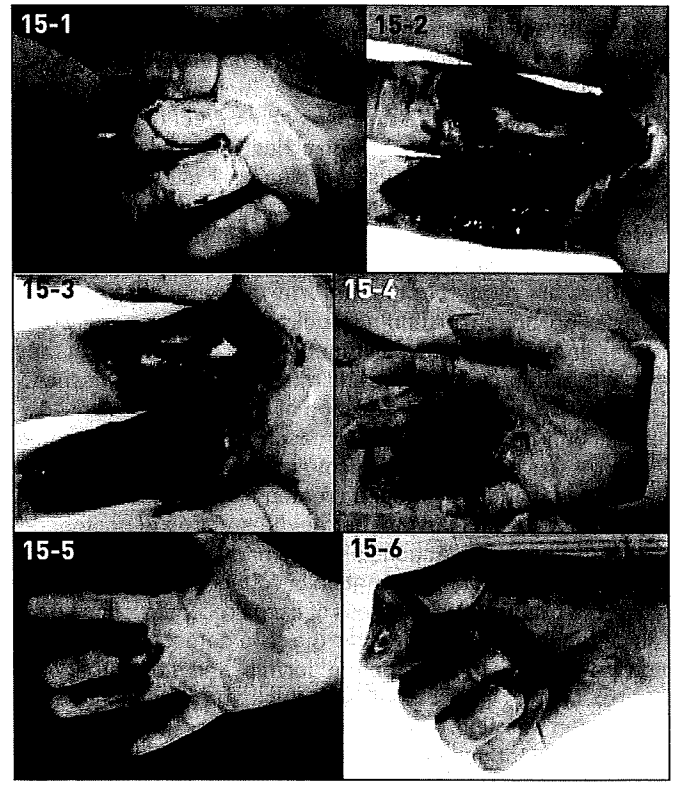

Figure 15-1. First examination of case 7. The patient sustained a heat-press injury to the right middle and ring fingers. Figure 15-2. Intraoperative view showing that the deep flexor tendon was exposed after debridement. Figure 15-3. Two weeks after combination treatment. The tendon was almost covered with fresh granulation tissue.
Figure 15-4. Three weeks after the first surgery. Abundant granulation tissue had developed on the exposed flexor tendon surface. The patient underwent nerve and free skin grafting. Figure 15-5. The wound was completely resurfaced by two weeks after skin grafting.
Figure 15-6. The patient showed a return of flexor function of the ring and middle fingers after undergoing tenolysis surgery.

Discussion

The resurfacing of skin wounds or ulcers is one of the most important and interesting problems for every clinician, because such wounds and ulcers will cause infection, exudates, odors, and bleeding, which decrease the patient's quality of life. Chronic ulcers may sometimes prevent the patient from living at home.[23]

The development of artificial dermis composed of atelocollagen sponge and a silicone membrane has markedly improved wound healing treatment, especially in emergent treatment for open injuries. Previously, resurfacing the tendon- and bone-exposed wounds with skin defects required pedicle or free flaps, showing high morbidity at the donor site, requiring skillful micro- or plastic surgeons, microsurgical instruments, and a great deal of time. Injured patients with life-threatening complications are sometimes unable to undergo major surgical treatment, which might lead to amputation of the extremities. Only the application of artificial dermis over the wounds allows surgeons to watch and wait until a second operation is performed several weeks later. In this way, delayed resurfacing surgery can be completed with free skin grafting only.

Regarding minor injury, fingertip injuries have been treated using microsurgical re-plantation, but 41% of patients showing treatment failure in the presence of crush or avulsion trauma are managed with the application of artificial dermis without the need for a subsequent free skin graft performed for functional or esthetic reasons.[24] Successful artificial dermis application can potentially reduce the need for microsurgery.

Another purpose of these permanent skin substitutes is to treat full-thickness skin defects as well as to improve the quality of the skin. The quality of regenerated dermal tissue was investigated, and it was concluded that the dermal regeneration of experimental full-thickness skin defects was significantly improved by treatment with artificial dermis containing large numbers of autologous fibroblasts.[25] Histological studies also indicated that atelocollagen-implanted wounds showed the formation of rete ridges and elongated dermal papillate processes, being similar to those of normal mucosa.[6] These structures are related to the maturity of the epidermal-dermal junction, and these findings indicate that the regenerated mucosa and scars would gain functions similar to those of the normal basement membrane and mucosal connective tissues.[26] The similarity of the construction of the regenerated tissue construction could be one of the reasons for the reduced contraction of scars following atelocollagen implantation. Minabe et al. stated that atelocollagen created a stable healing environment because it leads to the rapid resolution of postoperative inflammatory reactions and permits the aggregation of fibroblasts and the rapid formation of collagen fiber bundles.[11] Nakamura examined the process of tissue reconstruction after atelocollagen implantation over the skin defect and the histological features of the repaired dermis, and stated that the repaired dermis was formed with thick and folded collagen bundles and was clearly different from the scar tissue, resembling the normal dermis.[27] From these findings, it was suggested that the degree of scar contraction was less in the atelocollagen-implanted site, leading to the improvement of the skin quality.

Various modified usages of artificial dermis have been developed to improve the results of wound healing. Artificial dermis combined with vacuum-assisted closure (VAC) dressings for the management of complex soft tissue wounds was reported, showing favorable outcomes.[28] Combination treatment with bFGF and artificial dermis, being introduced previously, is also effective for preparing a favorable wound bed for skin grafting. The reciprocal, beneficial action of both bFGF and artificial dermis promote the proliferation and recruitment of fibroblasts, neovascularization, and synthesis of collagen fibers. Consequently, this method improves complex wounds and promotes the rapid preparation of a favorable wound bed. This relationship may be compared to a fish pot and ground bait *(Figure 16)*. The fish pot is the artificial dermis, the ground bait is bFGF, and fish are fibroblasts. Simply setting a fish pot will catch some fish. However, scattering ground bait into the fish pot will capture more fish. This is the concept of combination treatment with bFGF and artificial dermis.

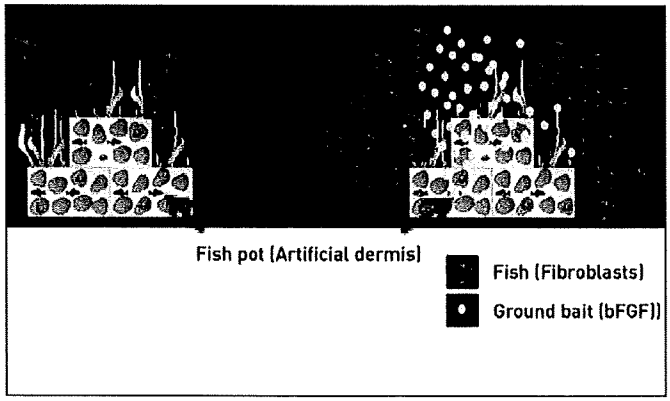

Figure 16. An allegory of the relationship between bFGF and artificial dermis.

Furthermore, this new method facilitates not only early dermal and epidermal wound healing, but also an improvement in the skin quality.[7,22,29] Combination treatment allows complex chronic ulcers, such as those induced by collagen vascular disease, to heal faster, where healing has not been facilitated by conventional treatments. This easy and effective treatment can be performed for almost all patients with skin wounds and chronic ulcers, excluding patients with cancer.

A disadvantage of treatment with artificial dermis is that it requires a two-step grafting procedure to achieve wound closure. To overcome this, Chu et al. investigated a single-step application of meshed, thin, split thickness autograft over meshed artificial dermis, and concluded that it facilitated a more rapid wound closure with less contraction and a more efficient use of graft donor skin than can be achieved with the commonly used two-step grafting procedure.[30]

Conclusion

The materials used and the techniques utilized to apply artificial dermis have been improving since collagen membranes were developed as an artificial skin in 1980.[31] Now, artificial dermis has become indispensable in the skin surgical field. Combination treatment has been shown to regenerate vivid granulation tissue and prepare a wound bed suitable for free skin grafting; such preparation is never achieved through conventional treatments. This method is straightforward, leads to minimal morbidity, and is useful for the treatment of all wounds, including complex chronic ulcers.

References

1. Douglass J. Wound bed preparation: a systematic approach to chronic wounds. *Br J Community Nurs* , 2003;8:26-34.

2. Fauci AS, Dale DC, Balow JE. Glucocorticoid therapy: Mechanisms of action and clinical considerations. *Ann Intern Med*, 1976;84:304-315.

3. Cho JY, Charbeneau TD. Coronal positioning of tissue previously treated with freeze-dried dura matter grafts.Report of a case. *J Periodontol.* 1986 Jan;57(1):35-38

3. Reuther JF, Wagner R, Braun B. Experimental study on the free transplantation of mucosa and lyophilised dura to the oral cavity.*J Maxillofac Surg.* 1978 Feb;6(1):64-69.

4. Stein MD, Salkin LM, Freedman AL, Glushko V. Collagen sponge as a topical hemostatic agent in mucogingival surgery. *J Periodontol.* 1985 Jan;56(1):35-38.

5. Fujioka M, Fujii T. Maxillary growth following atelocollagen implantation on mucoperiosteal denudation of the palatal process in young rabbits: implications for clinical cleft palate repair. *Cleft Palate Craniofac J.* 1997;34:297-308.

6. Akita S, Akino K, Imaizumi T, et al. The quality of pediatric burn scars is improved by early administration of basic fibroblast growth factor. *J Burn Care Res.* 2006;27:333-338.

7. Suzuki S, Kawai K, Ashoori F, et al. Long-term follow-up study of artificial dermis composed of outer silicone layer and inner collagen sponge. *Br J Plast Surg.* 2000; 53: 659-666.

8. Hom DB, Manivel JC. Promoting healing with recombinant human platelet-derived growth factor—BB in a previously irradiated problem wound. *Laryngoscope.* 2003; 113: 1566-1571.

9. Konisi J, Goto A, Osaki K,Koido M. A new type collagen matrix reconstructed self-connective tissue. *Jn Artif Organs* 1989;18:155-158.

References

10. Minabe M, Kodama T, Hori T, Watanabe Y. Effect of atelocollagen on the wound healing reaction following palatal gingivectomy in rats. *J Periodontal Res* 1989;**24**:178-185.

11. Crigger M, Bogle GC, Garrett S, Gantes BG. Repair following treatment of circumferential periodontal defects in dogs with collagen and expanded polytetrafluoroethylene barrier membranes. *J Periodontol.* 1996 Apr;**67**(4):403-413.

12. Aichelmann-Reidy ME, Yukna RA, Evans GH, Nasr HF, Mayer ET. Clinical evaluation of acellular allograft dermis for the treatment of human gingival recession. *J Periodontol.* 2001 Aug;**72**(8):998-1005.

13. McFarlane RM, Wermuth RE. The use of hyperbaric oxygen to prevent necrosis in experimental pedicle flaps and composite skin grafts. *Plast Reconstr Surg* 1966;**37**:422-430.

14. Pruitt BA Jr, Levine NS. Characteristics and uses of biologic dressings and skin substitutes. *Arch Surg.* 1984 Mar;**119**(3):312-322.

15. Wang HJ, Chou TD, Tsou TL, Chen TM, Chen SL, Chen SG, Wei LG, Yeh KJ, Ko YH, Wang CS, Lee WH. The application of new biosynthetic artificial skin for long-term temporary wound coverage. *Burns.* 2005 Dec;**31**(8):991-997.

16. Wilensky JS, Rosenthal AH, Bradford CR, Rees RS. The use of a bovine collagen construct for reconstruction of full-thickness scalp defects in the elderly patient with cutaneous malignancy. *Ann Plast Surg.* 2005 Mar;**54**(3):297-301.

17. Douglass J. Wound bed preparation: a systematic approach to chronic wounds. *Br J Community Nurs* 2003;**8**:26-34.

18. Fauci AS, Dale DC, Balow JE. Glucocorticoid therapy: Mechanisms of action and clinical considerations. *Ann Intern Med* 1976; **84**:304-315.

19. Hom DB, Manivel JC. Promoting healing with recombinant human platelet-derived growth factor—BB in a previously irradiated problem wound. *Laryngoscope.* 2003; **113**: 1566-1571.

20. Palmer-Kazen U, Wariaro D, Luo F, et al. Vascular endothelial cell growth factor and fibroblast growth factor 2 expression in patients with critical limb ischemia. *J Vasc Surg.* 2004; **39**: 621-628.

21. Marks MG, Doillon C, Silver FH. Effects of fibroblasts and basic fibroblast growth factor on facilitation of dermal wound healing by type I collagen matrices. *J Biomed Mater Res.* 1991;**25**:683-696.

22. Bird C.Managing malignant fungating wounds. *Prof Nurse.* 2000;**15**:253-256.

23. Li J, Guo Z, Zhu Q, Lei W, Han Y, Li M, Wang Z. Fingertip replantation: determinants of survival. *Plast Reconstr Surg.* 2008 Sep;**122**(3):833-839.

24. Lamme EN, Van Leeuwen RT, Brandsma K, Van Marle J, Middelkoop E. Higher numbers of autologous fibroblasts in an artificial dermal substitute improve tissue regeneration and modulate scar tissue formation. *J Pathol.* 2000 A;**190**(5):595-603.

25. The epidermal-dermal junction. Briggaman RA, Wheeler CE Jr. *J Invest Dermatol.* 1975 Jul;**65**(1):71-84.

26. Nakamura T, Teramachi M, Sekine T, Kawanami R, Fukuda S, Yoshitani M, et al. Artificial trachea and long term follow-up in carinal reconstruction in dogs. *Int J Artif Organs.* 2000 Oct;**23**(10):718-724.

27. Helgeson MD, Potter BK, Evans KN, Shawen SB. Bioartificial dermal substitute: a preliminary report on its use for the management of complex combat-related soft tissue wounds. *J Orthop Trauma.* 2007 Jul;**21**(6):394-399.

28. Akita S, Akino K, Imaizumi T, Hirano A. A basic fibroblast growth factor improved the quality of skin grafting in burn patients. *Burns.* 2005 Nov;**31**(7):855-858.

29. Chu CS, McManus AT, Matylevich NP, Goodwin CW, Pruitt BA Jr. Integra as a dermal replacement in a meshed composite skin graft in a rat model: a one-step operative procedure. *J Trauma.* 2002 Jan;**52**(1):122-129.

30. Yannas IV, Burke JF. Design of an artificial skin. I. Basic design principles. *J Biomed Mater Res.* 1980 Jan;**14**(1):65-81.

各論

人工真皮の応用

藤岡正樹
国立病院機構長崎医療センター形成外科　医長

治療(J.Therap.)別刷
Vol.91, No.2 〈2009.2〉
株式会社 南山堂

各 論

人工真皮の応用

藤岡正樹
国立病院機構長崎医療センター形成外科　医長

プライマリ・ケアにおけるポイント

人工真皮は，全層皮膚欠損創に貼付することで母床や創縁から線維芽細胞・毛細血管が侵入・増生し，新たにコラーゲン線維が産生され真皮様の肉芽組織に置き換わるという，従来になかったユニークな特性をもった創傷治療材料である．この特性を生かして，骨や腱の露出した創に対してでさえ，植皮などの簡便な処置で創閉鎖ができるようになってきた．このような人工真皮のプライマリ・ケアでの使用は，外傷に対する初期治療の新しい選択肢としてすでに確立している．また，指尖損傷などの小範囲の皮膚欠損創では，植皮を追加しなくても整容的・機能的に良好な創の治療がなされる．さらに，従来は治療することが困難であった難治性潰瘍に対してbFGFとの併用療法で良好な結果を得ている．

このように，従来は皮弁を使用した比較的高度な手術を要した皮膚欠損創に対して，人工真皮を使用した治療では，恵皮部の犠牲が最小限で簡便な治療ができる．しかしながら，多くの場合で二次的に植皮術などの手術を要すること，良好な肉芽が形成されるまでに約2週間かかるため創治癒まで治療期間が長くなることが欠点である．

Ⅰ 人工真皮の構造と作用機序

人工真皮は，真皮の主な構成成分であるコラーゲンをウシやブタから抽出し，スポンジ状に合成したもので，表層にシリコンシートを貼った2層構造を呈している．これを真皮欠損創に貼付すると，コラーゲンスポンジを足場とし，自己の線維芽細胞や毛細血管の侵入・増殖を促し，肉芽組織を構築する[1]．生体内安定性が高く，細胞親和性に優れた人工真皮によって増生した肉芽組織はコラーゲン線維の配列が正常真皮と似ており，また粘膜面に貼付して上皮化した場合epidermal-der-

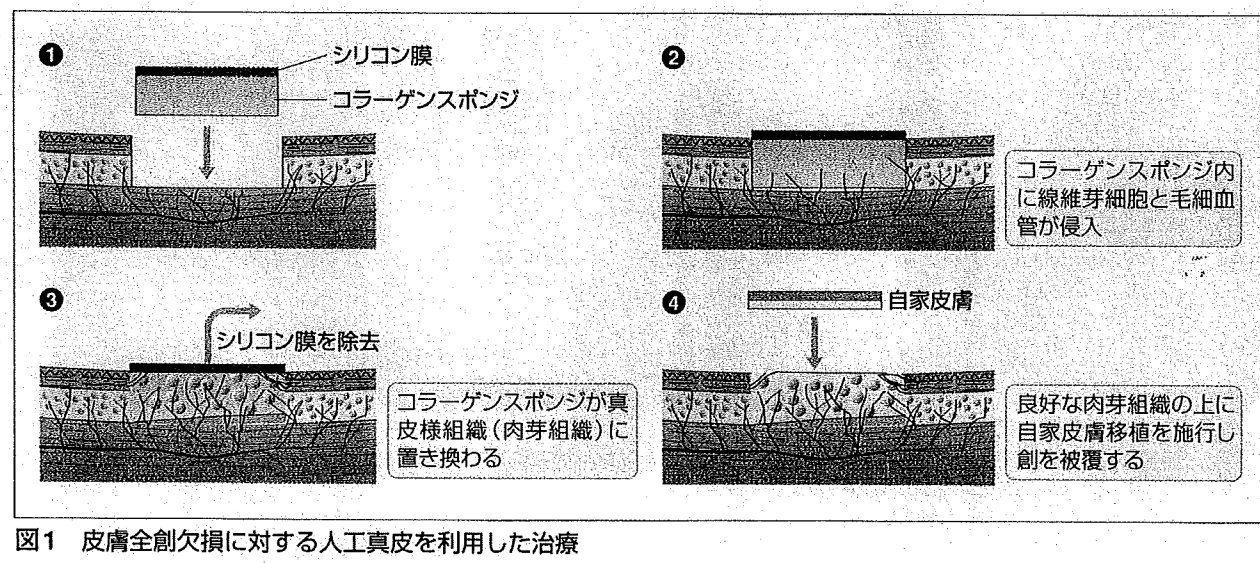

図1　皮膚全創欠損に対する人工真皮を利用した治療

mal junction様の構造を有することから真皮様組織と呼ばれ，通常の瘢痕組織と比べて拘縮が軽度であることが知られている[1~3]．しかし，人工真皮自体は表皮細胞を含まないため，上皮化を得るためには小範囲の創の場合を除いて自家皮膚移植を行う必要がある(図1)．わが国ではテルダーミス®(オリンパステルモバイオマテリアル株式会社)とペルナック®(グンゼ株式会社)が発売されている．

Ⅱ 人工真皮の臨床適応

1 口腔粘膜欠損創の被覆

そもそも歯科口腔外科領域での口腔内粘膜欠損に頻用されており[4]，図2で示すように，形成外科分野でも口蓋裂手術後の口蓋骨露出創に対して貼付し，早期創閉鎖や創の拘縮予防に効果をあげている[1]．人工真皮を口腔粘膜面に用いる場合，創面の速やかな粘膜上皮化が見られ，植皮を必要としない場合が多い．

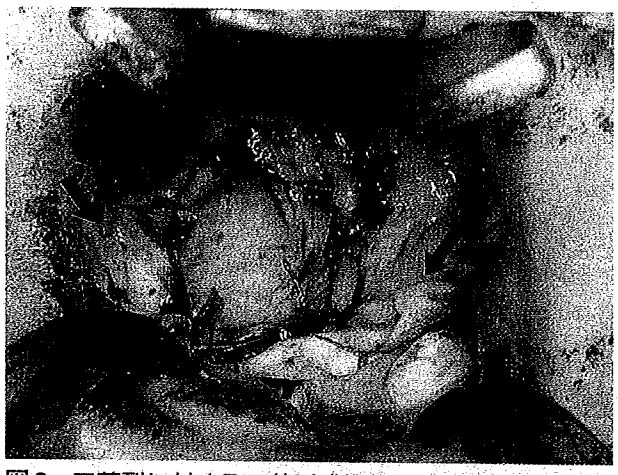

図2 口蓋裂に対する口蓋形成術後の骨露出創に対する人工真皮貼付例
矢印が貼付された人工真皮である．(→口絵36)

2 骨・腱露出創の被覆

骨や腱の表面は血行に乏しく植皮片の生着が望めないために，従来は骨露出創に対しては血行を有する有茎皮弁や遊離皮弁による被覆が必要とされてきた．しかし，骨露出面においてでさえも真皮様組織を形成する人工真皮のユニークな特性によって，これら重症外傷の初期治療は様変わりしつつある[5]．

図3は自動車に轢かれ右足関節部皮膚欠損創，腓骨遠位端骨折を受傷した症例である．腓骨遠位端に骨欠損があり，骨露出創となっていた(図3a, b)．露出した骨，腱膜上に人工真皮(テルダーミス®)を貼付し(図3c)，3週間後に骨，腱膜上に良好な肉芽の形成を見たため，殿部より採皮した薄

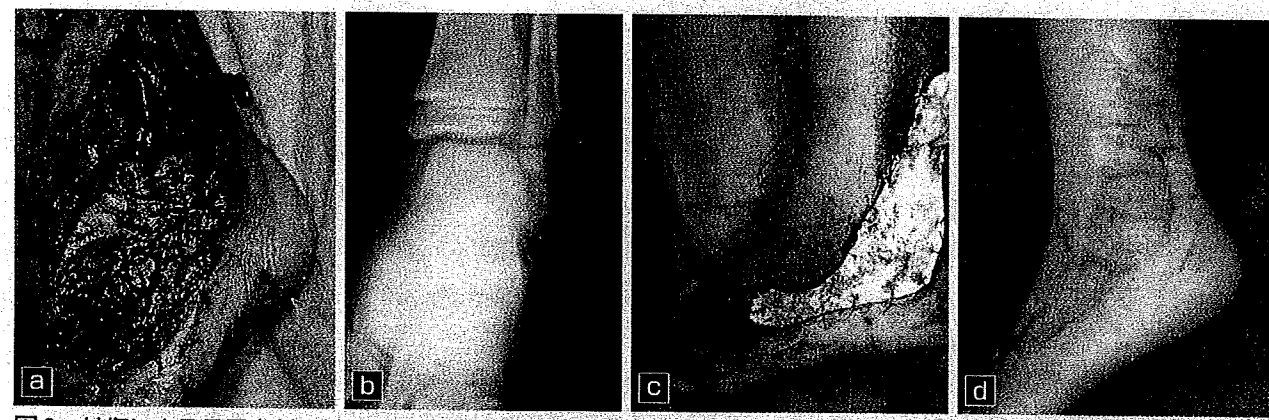

図3 外傷による骨露出創に対する人工真皮貼付例 (→口絵37)
a：初診時．右外踝足関節部皮膚欠損創・腓骨遠位端欠損を受傷し，骨・関節胞が露出した全層欠損創である(矢印)．
b：X線上，腓骨遠位端に骨欠損が認められた(矢印)．
c：デブリードマン後，人工真皮を貼付した．
d：植皮術後1年で全層植皮術に遜色のない柔らかな質感で治癒し，瘢痕拘縮・足関節運動制限も認められない．

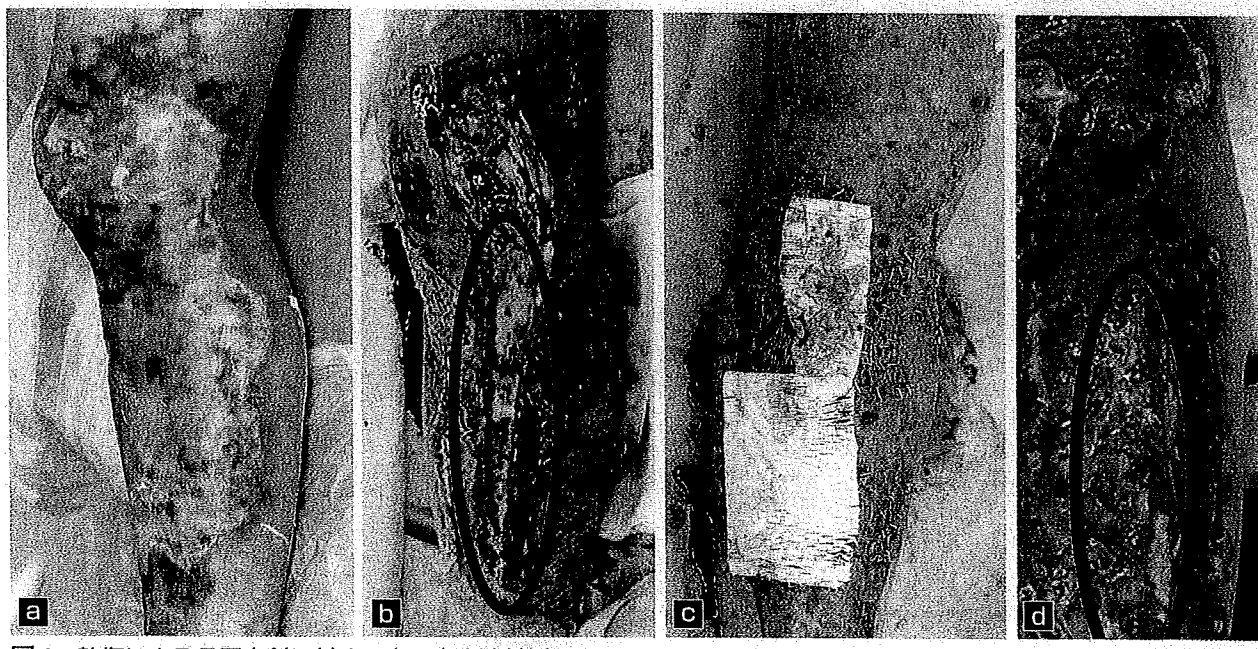

図4　熱傷による骨露出創に対する人工真皮貼付例　(→口絵38)
a：初診時．左下腿のⅢ度火炎熱傷のため膝から脛骨前面にかけて焼痂が付着している．
b：デブリードマン後，脛骨前面は脛骨露出創となった(線内)．
c：露出骨の上に人工真皮を貼付した．
d：2週間後に露出骨の上に良好な肉芽の形成を確認した(線内)．

めの分層皮膚で植皮術を行い，創は2週間後には閉鎖した．術後1年で全層植皮術に遜色のない柔らかな質感で治癒し，瘢痕拘縮・足関節運動制限も認められない(図3d)．

図4は左下腿のⅢ度火炎熱傷症例で，膝から脛骨前面にかけて皮膚全層の焼痂の付着を見る(図4a)．デブリードマンを施行したところ，脛骨前面は軟部組織の全層壊死に陥っており，広範囲の脛骨露出創となった(図4b)．骨皮質に小孔を開け，血行を確認したのちに露出した骨の上に人工真皮(ペルナック®)を貼付した(図4c)．2週間後に露出骨の上に良好な肉芽の形成を見たため(図4d)植皮術を施行，創を閉鎖した．

開放骨折や骨露出創の治療に関しては，可及的早期に創閉鎖を行うことを原則としているが，救急の現場では時間的・人的・設備的問題から一期的創閉鎖ができない場合がある．また，皮弁を用いて創閉鎖を行う場合には恵皮部の犠牲は避けられない問題である．このようなケースでは，筆者らは図3で紹介したように人工真皮を用いて良好な結果を得ている．人工真皮を貼付することによってGustilo-Anderson分類ⅢB，ⅢCの創をⅢAとすることができ，また恵皮部の犠牲もきわめて少なく簡便で有用な方法と考える．

3 小範囲の皮膚欠損創に対する被覆

一般に，人工真皮は真皮様組織を形成する目的で使用するため，二次的に植皮術を必要とするが，小範囲の皮膚欠損創に対して使用する場合は，人工真皮によって構築された良好な創床に速やかな上皮化を見る．この際には肉芽の造成のため陥凹変形が少なく，また保存的に治療する場合に比して瘢痕拘縮が少ないこと，恵皮部の犠牲が全くないことが利点である．

図5に上口唇犬咬傷により白唇部と赤唇部にまたがる2×1.5cmの全層皮膚欠損創の小児例を示す(図5a)．人工真皮(ペルナック®)を貼付したのちに植皮術を行うことなく保存的に上皮化を促した(図5b)．図5cに5ヵ月後の創の状態を示す．瘢痕はすでに成熟しており，肥厚することなくし

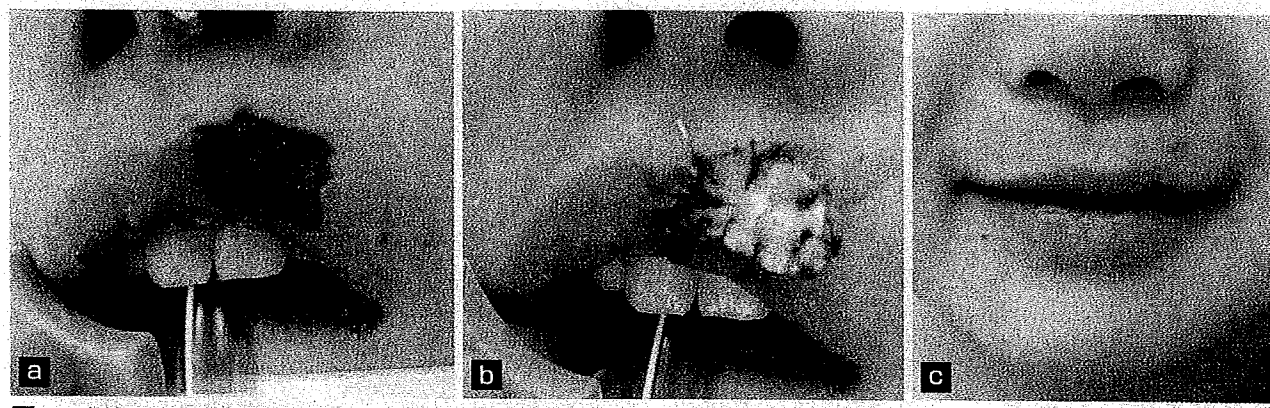

図5　小範囲皮膚欠損創に対する人工真皮貼付例
a：犬咬傷により白唇部と赤唇部にまたがる全層皮膚欠損創を負った．
b：人工真皮を貼付したのちに植皮術を行うことなく保存的に上皮化を促した．
c：5ヵ月後の創の状態．瘢痕は肥厚することなく拘縮も軽度である．
(→口絵39)

なやかである．拘縮も軽度でほぼ満足できる形態が得られた．

拘縮が少なく速やかに上皮化が図れることが，いわゆる創傷被覆材や生体被覆材（biological dressing material）と異なる特徴であるが，この性質を生かして指尖損傷の指断端に人工真皮を貼付する治療法が一般化しつつある（p.272）．本法を用いることで，やはり恵皮部の犠牲なしに簡便に良好な形態と機能を維持した指再建がなされるようになった[6]．

4 皮膚腫瘍完全切除生検後の一時的な被覆材としての使用

悪性腫瘍の可能性がある皮膚腫瘍を切除し，病理検査に提出する場合（excisional biopsy），一期的な創の縫縮が不可能であれば，植皮や皮弁を用いて創閉鎖を図る必要が出てくる．しかし，後日知らされる病理結果が悪性で追加の広範囲切除が必要となった場合，ドナーの犠牲を強いるばかりか，生検時の余分な創の扱いのため悪性細胞を播種させることになりかねない．この場合のテンポラリーな被覆材として，切除創に人工真皮を貼付しておくことがある．病理結果が出るまでの間，創傷処置が簡便で疼痛が少ないことが利点であり，悪性であった場合は二次的に広範囲切除と再建を，良性であれば形成された良好な肉芽の上に分層植皮を行う．

Ⅲ 人工真皮の新しい使い方（bFGFとの併用療法）

塩基性線維芽細胞成長因子（bFGF，フィブラスト®スプレー/科研製薬株式会社）は，血管内皮細胞，線維芽細胞，表皮細胞などさまざまな細胞の増殖を誘導することにより血管新生，創傷治癒促進する働きがある薬剤である．Akitaらは下腿難治性潰瘍に対して比較対照研究を行い，人工真皮とbFGFの併用により，下肢の創の早期治癒を促すばかりか，治癒後の瘢痕の質感も優れていると報告している[7]．また，飯田らは手指皮膚や爪床欠損対し人工真皮単独療法とbFGFとの併用療法との比較対照研究を行い，有意に併用療法が早期の創上皮化を見たと報告している[8]．すなわち図6で示すように，人工真皮貼付後bFGFを噴霧する併用療法では，従来の保存的加療では良好な創床を形成し得なかった難治癒性潰瘍に対して治癒を望める可能性を示唆する．

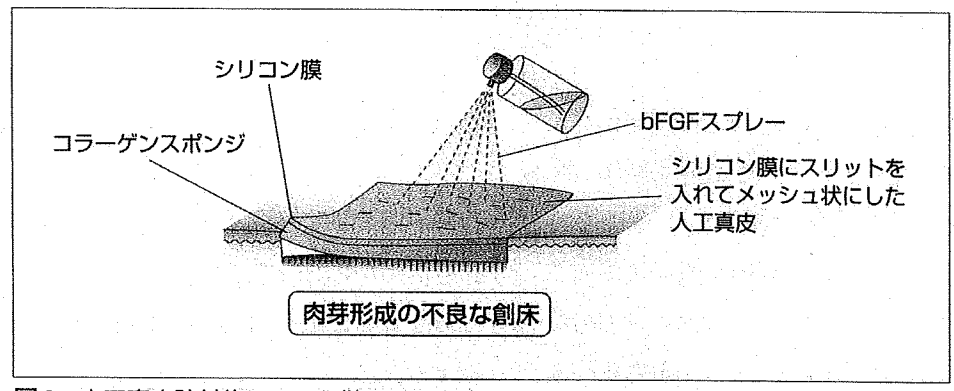

図6　人工真皮貼付後bFGFを併用する方法

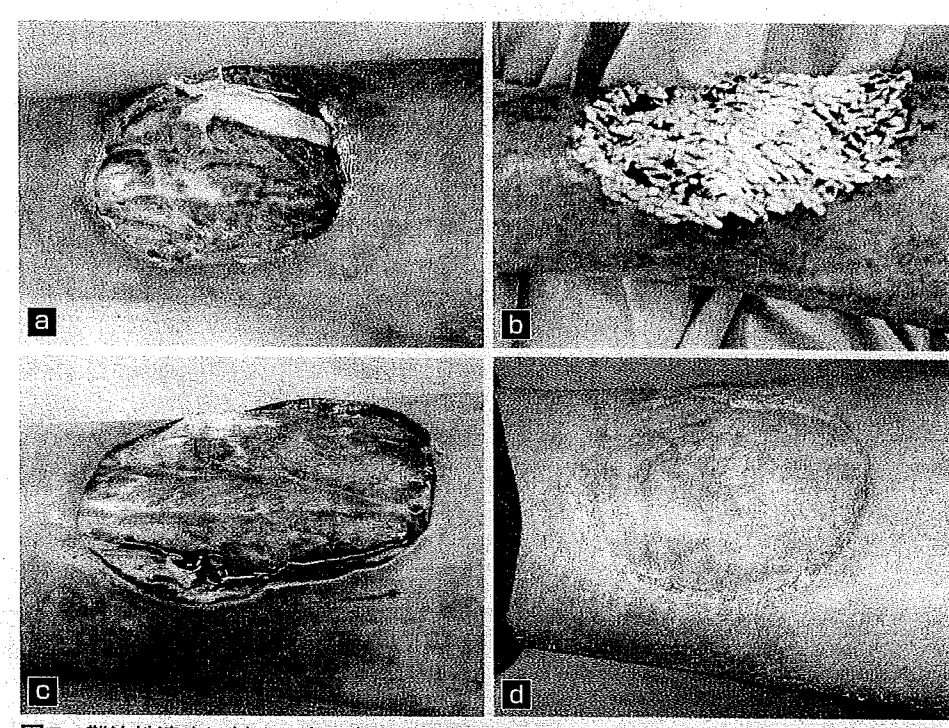

図7　難治性潰瘍に対する人工真皮とbFGF併用例　(→口絵40)
a：SLE患者に生じた下腿難治性潰瘍．通常の創洗浄では良好な創床が形成されない．
b：創に対して人工真皮を貼付し，bFGFを連日噴霧した．
c：併用療法開始2週間後に良好な肉芽による創床を形成した．
d：植皮手術後3年の経過で再発を認めていない．

図7はsystemic lupes erythematosis (SLE) を基礎疾患にもち，10年あまりプレドニゾロン20mg/日を服用した患者に生じた下腿難治性潰瘍である．通常のwound bed preparationの手法にのっとり，潰瘍に対してデブリードマン後2週間の創洗浄，wet to dry dressingを続けたが，良好な創床が形成されなかった(図7a)．この創に対し，人工真皮とbFGFの併用療法を施行した(図7b)．治療開始2週間後には良好な肉芽による創床を形成したので(図7c)，植皮手術を施行し治癒した．植皮は良好に生着し3年の経過で再発を認めていない(図7d)．

膠原病，ステロイド服用，透析，低栄養などのcompromised hostに生じる難治性潰瘍で従来の保存的治療で軽快しない症例に対し，人工真皮とbFGFの併用療法は簡便で有用な治療法となる可能性がある[9]．

おわりに

創傷被覆材と異なり，人工真皮は積極的に良好な肉芽組織を形成するため，救急外傷治療上，従来に比して簡便な処置で創閉鎖ができるようになってきた．さらに，難治性潰瘍に対してbFGFとの併用療法で良好な結果を得ている．しかし，多くの場合は二次的に植皮術などの手術を要すること，感染創には使用しにくいこと，良好な肉芽が形成されるまでに約2週間かかるため創治癒まで治療期間が長くなるなどの短所がある．人工真皮を用いた創閉鎖は有用な方法であるが，これらの特徴も考慮して適正な使用がなされることが望まれる．

参考文献

1) Fujioka M, Fujii T : Maxillary growth following athelocollagen implantation on mucoperiosterial denudation of palatal process in young rabbits imprication for clinical cleft palate repair. Cleft Palate Craniofac J, 34 : 297-308, 1997.

2) Briggaman RA, Wheeler CE Jr : Epidermolysis bullosa dystrophica-recessive : a possible role of anchoring fibrils in the pathogenesis. J Invest Dermatol, 65 : 203-211, 1975.

3) Minabe M, et al : Effects of atelocollagen on the wound healing reaction following palatal gingivectomy in rats. J Periodontal Res, 24 : 178-185, 1989.

4) 児玉利朗：インプラントの臨床が変わるティッシュマネージメント，第1版，医学情報社，東京，2008.

5) 藤岡正樹，大安剛裕：四肢の広範囲軟部組織欠損を伴う開放骨折に対する当科の治療方針．宮崎県医師会雑誌，24 : 156-161，1999.

6) 菅又　章，他：人工真皮を用いたfingernail salvage. 整形・災害外科，51 (2) : 215-223，2008.

7) Akita S, et al : The quality of pediatric burn scars is improved by early administration of basic fibroblast growth factor. J Burn Care Res, 27 : 333-338, 2006.

8) 飯田直成，他：人工真皮とbFGF製剤を併用した手指・手掌の皮膚及び爪床欠損の治療経験．形成外科，50 (4) : 451-457，2007.

9) Fujioka M : Combination treatment with basic fibroblast growth factor and artificial dermis improves complex wounds caused by collagen diseases with steroid use. Dermatologic Surgery (in press) .

Hemodialysis International 2009; **13**:168–171

Case Reports

Complex wounds tend to develop more rapidly in patients receiving hemodialysis because of diabetes mellitus

Masaki FUJIOKA, Kiyoshi OKA, Riko KITAMURA, Aya YAKABE
Department of Plastic and Reconstructive Surgery, National Nagasaki Medical Center, Nagasaki, Japan

Abstract
The number of patients requiring dialysis because of diabetes mellitus is increasing and such patients often have complex chronic wounds, which are difficult to heal. However, there are few retrospective studies of wounds requiring surgical treatment. We evaluated 14 patients receiving hemodialysis (HD) (8 because of diabetes and 6 because of other diseases) who had extremity wounds and underwent surgical treatment in our unit from 2004 through 2007. We investigated differences in the cause of wounds, and in the interval between the start of HD and wound development. Wounds in patients undergoing HD because of diabetes originated due to ischemia in 2 cases (25%), trauma in 2 cases (25%), and infection in 4 cases (50%). Seven of 8 wounds developed infection with methicillin-resistant *Staphylococcus aureus* (MRSA). Wounds in patients undergoing HD because of other diseases developed due to ischemia in 2 cases (33%) and trauma in 4 cases (67%). Three of 6 wounds developed infection and MRSA were isolated from 2 wounds. The interval between the start of HD and wound development was significantly shorter in patients with diabetes than in patients without diabetes. All patients with infectious wounds required immediate debridement. We conclude that patients receiving HD because of diabetes are likely to have more severe and rapidly developing wounds due to infections. Thus, they usually require immediate debridement before blood access shunt infection occurs.

Key words: Hemodialysis, diabetes mellitus, complex chronic wounds, surgical treatments

INTRODUCTION

The number of patients requiring hemodialysis (HD) because of obesity-related renal diseases such as diabetes mellitus (DM) is increasing.[1,2] Patients receiving HD often have complex chronic wounds, which are hard to heal because of complications of other diseases, including DM, calciphylaxis, collagen disease, arteriosclerosis obliterans, chronic anemia, and weakness of the skin.

Correspondence to: F. Masaki M.D., Department of Plastic and Reconstructive Surgery, National Hospital Organization Nagasaki Medical Center, 1001-1 Kubara 2, Ohmura City, Nagasaki, Japan Zip 856-8562.
E-mail: mfujioka@nmc.hosp.go.jp

We report our 4-year experience with 14 patients receiving HD who had chronic skin ulcers. In addition, we investigated the differences in the characteristics between patients receiving HD because of DM and patients receiving HD because of other diseases.

MATERIALS AND METHODS

Fourteen patients receiving HD who had chronic wounds of the limbs underwent surgical treatment in our unit from 2004 through 2007. Ages ranged from 52 to 74 years (mean age, 62.1 years). We investigated the originated disease, characteristics of wounds (diagnosis, site, cause, and size), the interval between the start of HD to the development of the wounds, complications, and the

Table 1 Profiles and clinical status of patients undergoing hemodialysis (HD) who had extremity ulcers

Patient number	Sex	Age	Originated disease	Wound diagnosis	Site of wound	Cause of wound	Wound size (cm)	Surgery	Infection and culture	Immediate debridement	HD duration (years)	Complication
1	M	53	DM	Ischemic skin necrosis	Rt step	Ischemia	7 × 5	Amputation	MRSA	–	8	HT, ASO, sepsis
2	F	68	DM	Ischemic skin necrosis	Rt step	Ischemia	2 × 2	FSG	—	–	4	HT, ASO
3	M	56	DM	Burn	Lt leg	Trauma	5 × 3	Amputation	MRSA	+	4	Angina, sepsis
4	M	58	DM	Pressure ulcer	Rt thigh	Trauma	10 × 7	Flap	MRSA	+	2	Mental disorder
5	F	70	DM	Necrotizing fasciitis	Lt heel	Infection	11 × 5	FSG	MRSA	+	1	HT
6	F	55	DM	Osteomyelitis	Rt index finger	Infection	2 × 2	Amputation	MRSA	+	2	Sepsis
7	M	65	DM	Necrotizing fasciitis	Lt leg	Infection	15 × 5	FSG	MRSA	+	1	HT
8	F	74	DM	Gangrene	Rt thigh	Infection	5 × 3	FSG	MRSA	+	4	HT
9	F	69	CGN	Skin necrosis (instillation into subcutaneous)	Rt leg	Trauma	5 × 4	FSG	*Streptococcus Constellatus*	–	4	peritonitis
10	F	58	CGN	Postoperative skin necrosis	Rt leg	Trauma	3 × 2	FSG	—	–	16	HT, Achilles' tendon rupture
11	F	62	CGN	Postoperative skin necrosis	Lt thigh	Trauma	2 × 2	Suturing	—	–	2	HT, hypothyroidism
12	M	65	CGN	Ischemic necrosis	Both legs	Ischemia	13 × 5	Amputation	MRSA	–	14	HT, ASO, sepsis
13	M	65	Polycystic kidney	Ischemic skin necrosis	Rt toe	Ischemia	3 × 2	Amputation	—	–	9	HT, ASO
14	F	52	SLE	Laceration	Lt hand	Trauma	5 × 4	Amputation	MRSA	+	32	Chronic hepatitis, sepsis, steroid

ASO=arteriosclerosis obliterans; CGN=chronic glomerular nephritis; DM=diabetes mellitus; FSG=free skin grafting; HT=hypertension; Lt=left; MRSA=methicillin-resistant *Staphylococcus aureus*; Rt=right; SLE=systemic lupus erythematosis.