vascular index. Tohoku J Exp Med, 2009; 218: 115-119
44) Uehara G, Takeda H: Relative effects of telmisartan, candesartan and losartan on alleviating arterial stiffness in patients with hypertension complicated by diabetes mellitus: an evaluation using the cardio-ankle vascular index (CAVI). J Int Med Res, 2008; 36: 1094-1102
45) Kinouchi K, Ichihara A, Sakoda M, Kurauchi-Mito A, Murohashi-Bokuda K, Itoh H: Effects of telmisartan on arterial stiffness assessed by the cardio-ankle vascular index in hypertensive patients. Kidney Blood Press Res, 2010; 33: 304-312
46) Bokuda K, Ichihara A, Sakoda M, Mito A, Kinouchi K, Itoh H: Blood pressure-independent effect of candesartan on cardio-ankle vascular index in hypertensive patients with metabolic syndrome. Vasc Health Risk Manag, 2010; 6: 571-578
47) Sasaki H, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohhira M, Oyama T, Miyashita Y, Shirai K: Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. J Atheroscler Thromb, 2009; 16: 568-575
48) Miyashita Y, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effects of olmesartan, an angiotensin II receptor blocker, and amlodipine, a calcium channel blocker, on Cardio-Ankle Vascular Index (CAVI) in type 2 diabetic patients with hypertension. J Atheroscler Thromb, 2009; 16: 621-626
49) Ishimitsu T, Numabe A, Masuda T, Akabane T, Okamura A, Minami J, Matsuoka H: Angiotensin-II receptor antagonist combined with calcium channel blocker or diuretic for essential hypertension. Hypertens Res, 2009; 32: 962-968
50) Kinouchi K, Ichihara A, Sakoda M, Kurauchi-Mito A, Itoh H: Safety and benefits of a tablet combining losartan and hydrochlorothiazide in Japanese diabetic patients with hypertension. Hypertens Res, 2009; 32: 1143-1147
51) Nagayama D, Saiki A, Endo K, Yamaguchi T, Ban N, Kawana H, Ohira M, Oyama T, Miyashita Y, Shirai K: Improvement of cardio-ankle vascular index by glimepiride in type 2 diabetic patients. Int J Clin Pract, 2010; 64: 1796-1801
52) Ohira M, Endo K, Oyama T, Yamaguchi T, Ban N, Kawana H, Nagayama D, Nagumo A, Saiki A, Murano T, Watanabe H, Miyashita Y, Shirai K: Improvement of postprandial hyperglycemia and arterial stiffness upon switching from premixed human insulin 30/70 to biphasic insulin aspart 30/70. Metabolism, 2010; 60: 78-85
53) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res, 2008; 31: 1347-1355
54) Miyashita Y, Endo K, Saiki A, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effects of pitavastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, on cardio-ankle vascular index in type 2 diabetic patients. J Atheroscler Thromb, 2009; 16: 539-545
55) Satoh N, Shimatsu A, Kotani K, Himeno A, Majima T, Yamada K, Suganami T, Ogawa Y: Highly purified eicosapentaenoic acid reduces cardio-ankle vascular index in association with decreased serum amyloid A-LDL in metabolic syndrome. Hypertens Res, 2009; 32: 1004-1008
56) Miyashita Y, Endo K, Saiki A, Ban N, Nagumo A, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effect of ezetimibe monotherapy on lipid metabolism and arterial stiffness assessed by cardio-ankle vascular index in type 2 diabetic patients. J Atheroscler Thromb, 2010; 17: 1070-1076
57) Shirai K: Obesity as the core of the metabolic syndrome and the management of coronary heart disease. Curr Med Res Opin, 2004; 20: 295-304
58) Satoh N, Shimatsu A, Kato Y, Araki R, Koyama K, Okajima T, Ooshim M,Kotani K, Ogawa Y: Evaluation of the cardio-ankle vascular index, anew indicator of arterial stiffness independent of blood pressure, inobesity and metabolic syndrome. Hypertention Res, 2008; 31: 1921-1930
59) Ohashi N, Ito C, Fujikawa R, Yamamoto H, Kihara Y, Kohno N: The impact of visceral adipose tissue and high-molecular weight adiponectin on cardio-ankle vascular index in asymptomatic Japanese subjects. Metabolism, 2009; 58: 1023-1029
60) Kumagai T, Kasai T, Kato M, Naito R, Maeno K, Kasagi S, Kawana F, I, Shiwata S, Narui K: Establishment of the cardio-ankle vascular index in patients with obstructive sleep apnea. Chest, 2009; 136: 779-786
61) Lü YH, He ZM, Dong XS, Li J, Han X, An P, Wang L, He QY, Han F: Effects of short-term continuous positive airway pressure treatment on arterial stiffness in patients with obstructive sleep apnea hypopnea syndrome. Zhonghua Yi Xue Za Zhi, 2008; 88: 1189-1191
62) Noike H, Nakamura K, Sugiyama Y, Iizuka T, Shimizu K, Takahashi M, Hirano K, Suzuki M, Mikamo H, Nakagami T, Shirai K: Changes in cardio-ankle vascular index in smoking cessation. J Atheroscler Thromb, 2010; 17: 517-525
63) Sato H, Miida T, Wada Y, Maruyama M, Murakami S, Hasegawa H, Kuroda T, Narita I, Nakano M, Gejyo F: Atherosclerosis is accelerated in patients with long-term well-controlled systemic lupus erythematosus (SLE). Clin Chim Acta, 2007; 385: 35-42
64) Masugata H, Senda S, Himoto T, Murao K, Dobashi H, Kitano Y, Okuyama H, Inukai M, Hosomi N, Kohno M, Nishiyama Y, Kohno T, Goda F: Detection of increased arterial stiffness in a patient with early stage of large vessel vasculitis by measuring cardio-ankle vascular index. Tohoku J Exp Med, 2009; 219: 101-105
65) Masugata H, Senda S, Dobashi H, Himoto T, Murao K, Okuyama H, Inukai M, Hosomi N, Kohno M, Nishiyama Y, Kohno T, Goda F: Cardio-ankle vascular index for evaluating immunosuppressive therapy in a patient with aortitis syndrome. Tohoku J Exp Med, 2010; 222: 77-81
66) Wakabayashi I, Masuda H: Association of acute-phase reactants with arterial stiffness in patients with type 2 diabetes mellitus. Clin Chim Acta, 2006; 365: 230-235
67) Torisu T, Takata Y, Ansai T, Matsumoto T, Sonoki K, Soh I,

Awano S, Yoshida A, Hamasaki T, Kagiyama S, Nakamichi I, Ohsumi T, Toyoshima K, Nishihara T, Iida M, Takehara T: Possible association of atrophic gastritis and arterial stiffness in healthy middle-aged Japanese. J Atheroscler Thromb, 2009; 16: 691-697

68) Wu CF, Kuo IC, Su TC, Li YR, Lin LY, Chan CC, Hsu SC: Effects of personal exposure to particulate matter and ozone on arterial stiffness and heart rate variability in healthy adults. Am J Epidemiol, 2010; 171: 1299-1309

69) Mizuguchi Y, Oishi Y, Tanaka H, Miyoshi H, Ishimoto T, Nagase N, Oki T: Arterial stiffness is associated with left ventricular diastolic function in patients with cardiovascular risk factors: early detection with the use of cardio-ankle vascular index and ultrasonic strain imaging. J Card Fail, 2007; 13: 744-751

70) Sakane K, Miyoshi T, Doi M, Hirohata S, Kaji Y, Kamikawa S, Ogawa H, Hatanaka K, Kitawaki T, Kusachi S, Yamamoto K: Association of new arterial stiffness parameter, the cardio-ankle vascular index, with left ventricular diastolic function. J Atheroscler Thromb, 2008; 15: 261-268

71) Masugata H, Senda S, Goda F, Yamagami A, Okuyama H, Kohno T, Hosomi N, Yukiiri K, Noma T, Kiyomoto H, Murao K, Nishiyama A, Kohno M: Tissue Doppler echocardiography for predicting arterial stiffness assessed by cardio-ankle vascular index. Tohoku J Exp Med, 2009; 217: 139-146

72) Masugata H, Senda S, Okuyama H, Murao K, Hosomi N, Inukai M, Iwado Y, Noma T, Kohno M, Goda F: Aortic annular velocity assessed by tissue Doppler echocardiography as a potential parameter of arterial stiffness. Tohoku J Exp Med, 2010; 221: 169-174

73) Uurtuya S, Taniguchi N, Kotani K, Yamada T, Kawano M, Khurelbaatar N, Itoh K, Lkhagvasuren T: Comparative study of the cardio-ankle vascular index and ankle-brachial index between young Japanese and Mongolian subjects. Hypertens Res, 2009; 32: 140-144

74) Uurtuya S, Kotani K, Taniguchi N, Yoshioka H, Kario K, Ishibashi S, Yamada T, Kawano M, Khurelbaatar N, Itoh K, Lkhagvasuren T: Comparative study of atherosclerotic parameters in Mongolian and Japanese patients with hypertension and diabetes mellitus. J Atheroscler Thromb, 2010; 17: 181-188

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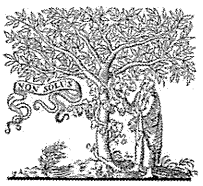

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Association between plate location and plate removal following facial fracture repair☆

Yoshitaka Kubota [a,*], Tomoaki Kuroki [b], Shinsuke Akita [a], Tomoe Koizumi [a], Masakazu Hasegawa [a], Naoaki Rikihisa [a], Nobuyuki Mitsukawa [a], Kaneshige Satoh [a]

[a] *Department of Plastic Surgery, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba-city, Chiba #260-8677, Japan*
[b] *Department of Plastic Surgery, Narita Red Cross Hospital, 90-1, Iida-cho, Narita-city, Chiba #286-8523, Japan*

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KEYWORDS
Facial fracture;
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Summary *Background:* Titanium-based plates used to repair facial fractures are sometimes removed despite their high biocompatibility. Local discomfort can lead to plate removal surgery. Local discomfort may differ according to patient characteristics, tissue properties and plate thickness; however, little is known about the relationship between these conditions and plate removal.
Methods: We performed a hospital-based, retrospective cohort study of patients who underwent internal fixation for facial or frontal bone fracture. To identify factors associated with plate removal, we used multivariate logistic regression models.
Results: Data from 138 patients were analysed. All plates were made of commercially pure titanium, and all screws were made of titanium, 6% aluminium and 4% vanadium alloy. Plate thickness was 1.2 mm or 0.6 mm. Among plate locations, the frontozygomatic suture showed the highest percentage of complications (84%, 86 of 102 patients). The majority consisted of palpability and visibility. In patients who underwent plate removal ($n = 96$), all plates and screws were removed successfully. All plate-related complications were resolved after plate removal. No complications were introduced by plate removal. Plates 1.2 mm in thickness on the frontozygomatic suture had a relative risk of complications 2.48 times (95% confidence interval, 1.13–5.43) that of plates 0.6 mm in thickness. By multivariate analysis, the presence of plates on the frontozygomatic suture was a significant and independent risk factor for removal. Patients with plates on the frontozygomatic suture had a risk of plate removal 3.95 times (95% confidence interval, 1.55–10.07; $P < 0.01$) that of patients without plates on the frontozygomatic suture.

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* Corresponding author. Tel./fax: +81 43 226 2316.
E-mail address: kubota-cbu@umin.ac.jp (Y. Kubota).

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Conclusion: Plates on the frontozygomatic suture have a high rate of complications. Thick plates increase these risks. Patients with plates on the frontozygomatic suture are more likely to undergo plate removal surgery than patients without plates on the frontozygomatic suture.

Introduction

Titanium-based plates and screws are commonly used for facial or frontal bone fracture repair.[1] The formerly used stainless steel or cobalt–chromium alloy can introduce a risk of malignant tumour formation, corrosion, metal toxicity, allergy and interference with X-ray imaging, computed tomography and magnetic resonance imaging.[2–5] Titanium and its alloy are thought to be free of these problems.[2,6] Commercially available titanium-based plates and screws for facial fracture repair usually consist of plates made of commercially pure titanium, and screws made of titanium, 6% aluminium and 4% vanadium (Ti–6Al–4 V) alloy.[2] The aluminium and vanadium increases hardness.[7] Titanium and its alloy have higher biocompatibility and corrosion resistance than stainless steel or cobalt–chromium alloy.[8,9]

In spite of their high biocompatibility, titanium-based plates and screws can cause complications and are sometimes removed.[10–13] Some clinical evidence suggests that local complication rates after internal fixation of facial fractures are similar for both titanium-based plates and stainless steel plates.[10,14–17]

We hypothesised that the potential for plate-related complications differs according to facial location, because the physical properties of facial tissues vary widely with location. In addition, plates used for facial fracture repair have a variety of thicknesses, and the thickness of the plates may affect the local complications. Moreover, patient characteristics vary widely. However, little is known about the association between these differences in conditions and complications.

Objective

To clarify the differences in complications by location and thickness of plates used for facial or frontal bone fracture and to determine the factors related to plate removal.

Design, setting

We performed a hospital-based, retrospective cohort study. The study protocol was approved by the ethical committee of Narita Red Cross Hospital. Written informed consent was not required.

Patients and methods

Selection of patients and study protocol

Patients aged 15 years or older who underwent internal fixation for frontal or facial bone fracture at the Narita Red Cross Hospital from September 2000 to October 2007 were identified retrospectively from the operative register.

Medical records were analysed retrospectively for data regarding sex, age at injury, cause of injury, medical comorbidity, type of anaesthesia, American Society of Anaesthesiologists (ASA) physical status category at the time of the internal fixation operation,[18] type of fracture, indication for plate placement, location, manufacturer, and composition of plates and screws, thickness of plates, the number of plates, prophylactic antibiotic, duration of antibiotic therapy, complications caused by plates during the follow-up period, retention or removal of plates and screws and complications after plate removal. The composition of the plates and screws and the thickness of the plates were determined from information available from their manufacturers.

Definitions of the ASA physical status categories are as follows.

PS 1: A normal healthy patient. No organic, physiologic or psychiatric disturbances.
PS 2: A patient with mild systemic disease. Controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease and mild obesity.
PS 3: A patient with severe systemic disease. Poorly controlled hypertension or diabetes, stable angina, previous heart attack, controlled congestive heart failure, bronchospastic disease with intermittent symptoms and morbid obesity.

Assignation of the ASA physical status was routinely performed before the general anaesthesia for the internal fixation operation by anaesthesiologists, of which at least one was a senior.

Statistical analysis

Continuous variables were compared with Student's *t*-test under the condition that equal variances could be assumed by Levene's test. Categorical variables were compared with Fisher's exact probability test. Relative risks and 95% confidence intervals were obtained. Multivariate logistic regression analyses were used to identify factors associated with plate removal. Adjusted odds ratios and 95% confidence intervals were obtained. Goodness of fit for the models was determined with the Hosmer–Lemeshow test. All *P* values quoted are two tailed. *P* values less than 0.05 were considered to indicate statistical significance. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) software (version 13.0 J; SPSS, Chicago, IL, USA).

Results

A total of 138 patients met the criteria for the study. No absorbable osteosynthetic materials were used in the study period. All operations were undertaken by a single plastic surgical unit including one senior surgeon and three residents. Indications for plate placement were any displacement, any instability or possible instability by mastication. All internal fixation operations and all removal operations were performed under general anaesthesia. Co-morbidities of the patients were as follows: 28 patients were cigarette smokers, 15 patients had controlled hypertension, three patients had poorly controlled hypertension, six patients had diabetes, three patients had mild obesity, two patients had stable angina and one patient had previous heart attack. All patients received prophylactic antibiotic therapy. In all cases, one gram of cefazolin was administered intravenously just before starting the operation. After the operation, one gram of cefazolin was administered intravenously twice a day for 3 days.

All plates and screws were the products of Taguchi (Tokyo, Japan). All plates were made of commercially pure titanium and all screws were an alloy of titanium, 6% aluminium and 4% vanadium (Ti—6Al—4 V). Plates were 0.6 mm or 1.2 mm in thickness. Successful bone union was obtained in all cases.

During the study period, 345 titanium plates were place in 138 patients. The mean number of plates per patient was 2.5 plates (range: from two to 12 plates). The ranges of the number of plates by plate location were as follows: one to six on the frontal area, one to two on the nasal bridge, one on the frontozygomatic suture, one on the zygomaticomaxillary buttress, one on the piriform area, two on the mandibular angle, two to five on the mandibular body and two to three on the mandibular symphysis.

The types of the fracture patterns were as follows: four patients had a frontal bone fracture, seven patients had a naso-orbito-ethmoidal fracture, 99 patients had an orbito-zygomatic complex fracture, 41 patients had a maxillary fracture and 48 patients had a mandibular fracture.

Causes of injuries

Most fractures were caused by motor vehicle accidents. Fall was the second most common cause of injury. The number of patients by cause of injury was as follows: 82 (59%) patients were injured by motor vehicle accidents, 33 (24%) patients were injured in a fall, 12 (9%) patients were injured by blunt assault, 10 (7%) patients were injured in sports activity and two patients were injured by a horse kick. No fractures were caused by gunshot wounds. There were no pathological fractures.

Complications by locations

Complications with plates showed significant differences among plate locations (Figure. 1). The frontozygomatic suture showed the highest percentage of complications (84%, 86 of 102 patients). We performed a statistical comparison between the frontozygomatic suture and the infraorbital rim, because they are located near each other and both had relatively large sample sizes. The infraorbital rim showed a low percentage of complications (18%, 20 of 110 patients). Plates on the frontozygomatic suture had a relative risk of complications 4.64 times (95% confidence interval, 3.09—6.95; $P < 0.01$) that of plates on the infraorbital rim.

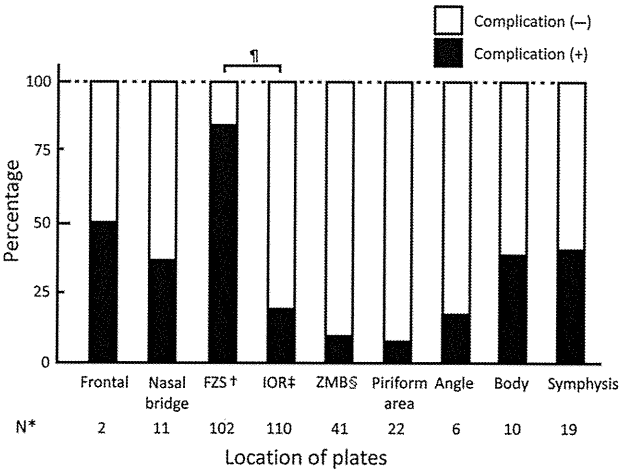

Figure. 1 Proportions of patients with complications by plate location: * The numbers of patients with plates by locations; † FZS denotes frontozygomatic suture; ‡ IOR denotes infraorbital rim § ZMB denotes zygomaticomaxillary buttress; ¶ Plates on the frontozygomatic suture have a relative risk of complications 4.64 times (95% confidence interval: 3.09—6.95; $P < 0.01$) that of plates on the infraorbital rim.

Palpability was the most frequently observed complication (Table 1). Visibility was the second most common complication. There were two cases of infection and one case of exposure.

Association between plate location and removal: univariate analyses

We performed statistical analyses to identify risk factors for plate removal by comparing patients who did not have their plates removed with those who had their plates removed. Removal of plates and screws was not done in 42 patients (retained group). The median follow-up period after internal fixation in the retained group was 382 days (range, from 310 to 701 days). Removal of plates and screws was performed in 96 patients (removed group). The median length of time between internal fixation and removal of plates in the removed group was 211 days (range, from 101 to 371 days). The median follow-up period after plate removal in the removed group was 257 days (range, from 184 to 402 days). In patients in the removed group, all plates and screws including both symptomatic and asymptomatic were removed simultaneously. All removal surgeries were performed with no major complications associated with the surgery itself or with the general anaesthesia. All plates and screws were removed successfully. In the removed group, all local complications related to the plates were resolved after plate removal. There were no local complications introduced by plate removal.

Table 1 Numbers of patients with complications by plate location.

Location	Infection	Exposure	Pain	Thermal hypersensitivity	Palpability	Visibility	Hypertrophic scar
Frontal	0	0	0	0	1	0	0
Nasal bridge	1	0	0	1	3	0	0
Frontozygomatic suture	0	0	2	7	69	15	1
Infraorbital rim	1	0	0	0	19	0	1
Zygomaticomaxillary buttress	0	1	1	1	1	0	0
Piriform area	0	0	0	0	2	0	0
Angle	0	0	0	0	1	0	0
Body	0	0	1	0	4	1	0
Symphysis	0	0	0	0	5	2	0

*Multiple answers are allowed.

There were no significant differences between the characteristics of the two patient groups (Table 2). In univariate analyses for the role of plate location, the frontozygomatic suture ($P = 0.02$), zygomaticomaxillary buttress ($P = 0.01$) and piriform area ($P = 0.01$) showed significant relationships with plate removal (Table 3).

Association between plate location and removal: multivariate analyses

We performed multivariate analyses using logistic regression models to adjust the associations between the explanatory variables for possible confounders. A multivariate analysis using a logistic regression model, where odds ratios were adjusted for age, sex, ASA physical status and the presence or absence of plates on every location showed that ASA physical status category (adjusted odds ratio, 0.23; 95% confidence interval, 0.10–0.58; $P < 0.01$) and the presence of the plates on the frontozygomatic suture (adjusted odds ratio, 33.31; 95% confidence interval, 3.48 to >99; $P < 0.01$) were significantly related to plate removal (Model 1 of Table 4). In the other model of multivariate logistic regression analysis, three locations that had shown significant relationships with plate removal in univariate analyses (Table 3: frontozygomatic suture, zygomaticomaxillary buttress and piriform area) were used (Model 2 of Table 4). Odds ratios were adjusted for age, sex, ASA physical status and the presence or absence of plates on these three locations. Model 2 also showed that a categorical increase in ASA physical status and the presence of plates on the frontozygomatic suture were significantly related to plate removal. The presence of plates on the frontozygomatic suture was an independent and significant risk factor for plate removal, and patients with plates on the frontozygomatic suture had a risk of plate removal 3.95 times (95% confidence interval, 1.55–10.07, $P < 0.01$) that of patients without plates on the frontozygomatic suture.

Table 2 Characteristics of the 138 patients in the study. Association with plate removal: univariate analyses.

Characteristics	Retained Group ($n = 42$)	Removed Group ($n = 96$)	*P* Value
Age (years)[a]	38 ± 17	36 ± 19	0.65
Sex (Number of Patients)			0.48
Female	6	20	
Male	36	76	
ASA PS (Number of Patients)[b]			0.19
PS 1	24	69	
PS 2	14	23	
PS 3	4	4	

PS 1 A normal healthy patient PS 2 A patient with mild systemic disease PS 3 A patient with severe systemic disease.
[a] Ages are presented as means ± SD. Student's t-test was used to compare the means of the two groups because equal variances could be assumed by Levene's test ($P = 0.33$).
[b] American Society of Anaesthesiologists Physical Status.

Effect of plate thickness

All plates used in the study period were made of commercially pure titanium and all screws were an alloy of titanium, 6% aluminium and 4% vanadium (Ti–6Al–4 V). Plates were 0.6 mm or 1.2 mm in thickness. Whether 0.6-mm or

Table 3 Association between plate location and removal surgery: univariate analyses.

Location (number of patients with plates)	Retained Group ($n = 42$)	Removed Group ($n = 96$)	*P* Value
Frontal	0	2	1.00
Nasal bridge	5	6	0.31
Frontozygomatic suture	25	77	0.02
Infraorbital rim	32	78	0.50
Zygomaticomaxillary buttress	18	19	0.01
Piriform area	12	10	0.01
Mandibular angle	0	6	0.18
Mandibular body	6	4	0.07
Mandibular symphysis	5	14	0.80

Table 4 Factors associated with plate removal: multivariate analyses.

Explanatory variable	Adjusted odds ratio	95% CI[b]	*P* value
Model 1[a]			
Age per 10 years increase	1.18	0.87–1.60	0.30
Male sex	4.38	1.18–16.22	0.27
A categorical increase in ASA PS[c]	0.23	0.10–0.58	<0.01
Frontal	>99	0.00 to >99	1.00
Nasal bridge	2.80	0.39–20.43	0.31
Frontozygomatic suture	33.31	3.48 to >99	<0.01
Infraorbital rim	0.12	0.01–1.73	0.12
Zygomaticomaxillary buttress	0.46	0.13–1.57	0.22
Piriform area	0.73	0.15–3.51	0.69
Mandibular angle	>99	0.00 to >99	1.00
Mandibular body	0.12	0.01–1.78	0.12
Mandibular symphysis	2.70	0.38–18.96	0.32
Model 2[a]			
Age per 10 years increase	1.05	0.80–1.36	0.74
Male sex	2.60	0.84–8.08	0.10
A categorical increase in ASA PS[c]	0.38	0.17–0.83	0.02
Frontozygomatic suture	3.95	1.55–10.07	<0.01
Zygomaticomaxillary buttress	0.43	0.14–1.37	0.15
Piriform area	0.67	0.17–2.68	0.57

[a] Odds ratios were adjusted for age, sex, ASA PS, and presence or absence of plates on all locations listed in the table. To evaluate trends in odds, ASA PS (ordinal variable) was modelled as single, continuous, independent variable. There was no evidence of lack of fit for the model in the Hosmer–Lemeshow goodness of fit test.
[b] CI denotes confidence interval.
[c] ASA PS denotes American Society of Anaesthesiologists Physical Status.

1.2-mm plates should be used was decided on a case-by-case basis depending on the surgeons' preferences and opinions.

There was a significant relationship between plate thickness and complication in the frontozygomatic suture. Plates 1.2 mm in thickness on the frontozygomatic suture had a relative risk of complications 2.48 times (95% confidence interval, 1.13–5.43; $P < 0.01$) that of plates 0.6 mm in thickness. Ninety-one patients had a 1.2-mm-thick plate fixed over their frontozygomatic suture. Among these 91 patients, 82 patients had complications related to plates on their frontozygomatic suture. Meanwhile, 11 patients had a 0.6-mm-thick plate fixed on frontozygomatic suture. Among these 11 patients, four patients had complications related to plates on the frontozygomatic suture.

In the analysis of the association between plate thickness and removal at the frontozygomatic suture, although the proportion of patients who underwent plate removal was higher for patients with plates of 1.2 mm in thickness than for those having plates 0.6 mm in thickness, it was not statistically significant (relative risk, 1.43; 95% confidence interval, 0.83–2.48; $P = 0.13$). Among 91 patients who had a 1.2-mm-thick plate fixed on their frontozygomatic suture, 71 patients had an operation to remove it. Meanwhile, among 11 patients who had a 0.6-mm-thick plate on frontozygomatic suture, six patients had a removal operation.

Discussion

The main causes of injury in our study were similar to those in other reports: motor vehicle accident, fall and blunt assault.[14,16,19–21] Unlike in other reports, none of our patients had injuries caused by gunshot wounds.[14,16,22] This might be the result of the very strict gun control in Japan.

Rates of complications caused by plates varied widely by plate location in our study. Plates on the frontozygomatic area had a tendency to cause more complaints than those on other areas, as in other studies.[13,15,23] Although the frontozygomatic suture and infraorbital rim are located near each other and are often fixed simultaneously in facial fracture repair, such as with zygomatic fractures, there was a significant difference in discomfort caused by plates at these locations. The difference in discomfort might be caused by differences in anatomical properties between the frontozygomatic area and the infraorbital area.[24,25] Because thin skin lies over the prominent bones, a plate on the frontozygomatic suture can be prone to palpability, bulging appearance, thermohypersensitivity and pain.

The presence of plates on the frontozygomatic suture was a significant and independent risk factor for plate removal in our study. Patients who had plates on the frontozygomatic suture were about four times more likely to undergo removal surgery. We suggest that the discomfort related to the plates

on the frontozygomatic suture might lead patients to undergo removal surgery and that the thickness of the plates on frontozygomatic suture is one of the factors linked to the high proportion of patients with discomfort on the frontozygomatic suture. Thus, the presence of plates on the frontozygomatic suture is a significant risk factor for plate removal.

Thicker plates on the frontozygomatic suture were related to more discomfort than were thinner plates in our study. Based on our study and other reports, the frontozygomatic suture is one of the most uncomfortable areas after internal fixation. Palpability was the most common complication related to a plate on the frontozygomatic suture in our study. Meanwhile, palpability is not regarded as a common adverse event in other reports. Measurements of palpability are prone to be subjective. Palpability revealed only by meticulous palpation or palpability without discomfort was not regarded as complication in our study. The use of thin plates is an option to reduce the discomfort caused by plates on the frontozygomatic suture, although there is controversy regarding their fixation strength.[11,26] Although it is difficult to conclude definite causality between plate thickness and complications because of the small sample size and observational nature of our study, currently, we always use a thin titanium plate on the frontozygomatic suture. We believe thin titanium plates can be beneficial for the rest of the upper facial area because the cortical bones there are thin. We do not believe that very rigid fixation strength is required for the upper face. For the mandible, we believe thick plates are better because of their fixation strength.

We had no patients in whom absorbable plates and screws were used in the study period. We believe that absorbable plates and screws are useful for paediatric craniofacial surgery patients. We also believe the fixation strength of absorbable plates and screws are sufficient for achieving bone union of fracture of the upper face in adults. However, for frontozygomatic suture, we prefer not to use absorbable plates and screws because of their thickness and the inflammation accompanying biodegradation.[27] Absorbable plates available in Japan have a thickness of 0.9, 1.0 and 1.4 mm. All of them are thicker than the thinnest titanium plate of 0.6 mm. It takes several years for absorbable plates to be degraded mainly by hydrolysis *in vivo*. Degradation is achieved not only by hydrolysis but also by inflammation. We think it undesirable that there is inflammation in thin skin over the frontozygomatic suture because it can lead to exposure or discomfort.

The overall rate of plate removal was 70% (96 of 138 patients) in our study. Three patients underwent plate removal surgery because of infection or exposure. It is difficult to compare these results with other reports, because plate removal policies vary.[13–17,23,28–30] We have a treatment principle that non-absorbable plates and screws used for facial or frontal bone fracture repair should be removed electively after serving their clinical functions. For plate removal, we usually remove all plates and screws. Unlike other countries, such as the United States, a considerable number of hospitals in Japan have a policy of elective complete removal. This difference in removal policy may result from a difference in perceived risks from foreign materials and a difference in medical care systems between countries.[7,8,31]

The rate of infection and exposure was 2% (three of 138 patients). Others have reported a per-patient infection and exposure rate of 3–9% after internal fixation of facial fractures under symptomatic removal intention.[15,17,23,32] Although it is difficult to make a simple comparison between our results and those of others, we think that the relatively low infection and exposure rate in our study is partially the result of our elective removal principle that can avoid preventable complications after bone healing. Islamoglu et al. reported that all infections were seen after bone union.[13] O'Connell et al. reported the lowest per-patient infection and exposure rate of 3% (15 of 535 patients) under a symptomatic removal policy.[32] We agree that careful preoperative, intraoperative and postoperative managements as indicated in their report are essential for preventing infection and exposure.

Complications related to the presence of plates were diminished after plate removal in all patients who underwent removal surgery. There were no complications introduced by plate removal. The removal of non-functioning plates did not appear to cause undue risk to patients in our study.

Patients with a higher category of ASA physical status were significantly more unlikely to undergo removal surgery. We suggest that reluctance to undergo more surgery with general anaesthesia is associated with hesitation about plate removal.

The observational nature of our study makes it difficult to infer causality. The generalisability of our data is unknown because the study was conducted at only one hospital.

Conclusions

Plates on the frontozygomatic suture cause high rates of complications. The presence of plates on the frontozygomatic suture is a significant and independent risk factor for plate removal after facial or frontal bone fractures. Thick plates on the frontozygomatic suture are associated with significantly higher rates of complications than thin ones. The use of thin plates is a possible choice for reducing complications related to plates on the frontozygomatic suture.

Conflict of interest

None.

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References

1. Soejima K, Sakurai H, Nozaki M, et al. Semi-closed reduction of tripod fractures of zygoma under intraoperative assessment using ultrasonography. *J Plast Reconstr Aesthet Surg* 2009;**62**: 499–505.
2. Haug RH. Retention of asymptomatic bone plates used for orthognathic surgery and facial fractures. *J Oral Maxillofac Surg* 1996;**54**:611–7.
3. Jackson IT, Adham MN. Metallic plate stabilisation of bone grafts in craniofacial surgery. *Br J Plast Surg* 1986;**39**:341–4.
4. von Domarus H. Stabilisation of the mandible by A.O. compression plate after mandibulotomy. *Br J Plast Surg* 1981; **34**:389–91.
5. Woodman JL, Black J, Nunamaker DM. Release of cobalt and nickel from a new total finger joint prosthesis made of vitallium. *J Biomed Mater Res* 1983;**17**:655–68.
6. Blake GB, MacFarlane MR, Hinton JW. Titanium in reconstructive surgery of the skull and face. *Br J Plast Surg* 1990;**43**: 528–35.
7. Merritt K, Margevicius RW, Brown SA. Storage and elimination of titanium, aluminum, and vanadium salts, in vivo. *J Biomed Mater Res* 1992;**26**:1503–15.
8. Woodman JL, Jacobs JJ, Galante JO, Urban RM. Metal ion release from titanium-based prosthetic segmental replacements of long bones in baboons: a long-term study. *J Orthop Res* 1984;**1**:421–30.
9. Manor Y, Chaushu G, Taicher S. Risk factors contributing to symptomatic plate removal in orthognathic surgery patients. *J Oral Maxillofac Surg* 1999;**57**:679–82.
10. Alpert B, Seligson D. Removal of asymptomatic bone plates used for orthognathic surgery and facial fractures. *J Oral Maxillofac Surg* 1996;**54**:618–21.
11. Kuvat SV, Cizmeci O, Bicer A, et al. Improving bony stability in maxillofacial surgery: use of osteogenetic materials in patients with profound (> or =5mm) maxillary advancement, a clinical study. *J Plast Reconstr Aesthet Surg* 2009;**62**:639–45.
12. Malata CM, McLean NR, Alvi R, et al. An evaluation of the Wurzburg titanium miniplate osteosynthesis system for mandibular fixation. *Br J Plast Surg* 1997;**50**:26–32.
13. Islamoglu K, Coskunfirat OK, Tetik G, Ozgentas HE. Complications and removal rates of miniplates and screws used for maxillofacial fractures. *Ann Plast Surg* 2002;**48**:265–8.
14. Chaushu G, Manor Y, Shoshani Y, Taicher S. Risk factors contributing to symptomatic plate removal in maxillofacial trauma patients. *Plast Reconstr Surg* 2000;**105**:521–5.
15. Francel TJ, Birely BC, Ringelman PR, Manson PN. The fate of plates and screws after facial fracture reconstruction. *Plast Reconstr Surg* 1992;**90**:568–73.
16. Murthy AS, Lehman Jr JA. Symptomatic plate removal in maxillofacial trauma: a review of 76 cases. *Ann Plast Surg* 2005;**55**:603–7.
17. Stone IE, Dodson TB, Bays RA. Risk factors for infection following operative treatment of mandibular fractures: a multivariate analysis. *Plast Reconstr Surg* 1993;**91**:64–8.
18. Mak PH, Campbell RC, Irwin MG, American Society of A. The ASA physical status classification: inter-observer consistency. American Society of Anesthesiologists. *Anaesth Intensive Care* 2002;**30**:633–40.
19. Lim LH, Lam LK, Moore MH, Trott JA, David DJ. Associated injuries in facial fractures: review of 839 patients. *Br J Plast Surg* 1993;**46**:635–8.
20. Back CP, McLean NR, Anderson PJ, David DJ. The conservative management of facial fractures: indications and outcomes. *J Plast Reconstr Aesthet Surg* 2007;**60**:146–51.
21. MacKinnon CA, David DJ, Cooter RD. Blindness and severe visual impairment in facial fractures: an 11 year review. *Br J Plast Surg* 2002;**55**:1–7.
22. Nguyen V, Wollstein R. Civilian gunshot wounds to the fingers treated with primary bone grafting. *J Plast Reconstr Aesthet Surg* 2009;**62**:e551–5.
23. Nagase DY, Courtemanche DJ, Peters DA. Plate removal in traumatic facial fractures: 13-year practice review. *Ann Plast Surg* 2005;**55**:608–11.
24. Lee JW. Treatment of enophthalmos using corrective osteotomy with concomitant cartilage–graft implantation. *J Plast Reconstr Aesthet Surg* 2010;**63**:42–53.
25. Chen CT, Lai JP, Chen YR, et al. Application of endoscope in zygomatic fracture repair. *Br J Plast Surg* 2000;**53**:100–5.
26. Kim MG, Kim BK, Park JL, et al. The use of bioabsorbable plate fixation for nasal fractures under local anaesthesia through open lacerations. *J Plast Reconstr Aesthet Surg* 2008;**61**:696–9.
27. Xia Z, Triffitt JT. A review on macrophage responses to biomaterials. *Biomed Mater* 2006;**1**:R1–9.
28. Brown JS, Trotter M, Cliffe J, Ward-Booth RP, Williams ED. The fate of miniplates in facial trauma and orthognathic surgery: a retrospective study. *Br J Oral Maxillofac Surg* 1989;**27**: 306–15.
29. Iizuka T, Lindqvist C, Hallikainen D, Paukku P. Infection after rigid internal fixation of mandibular fractures: a clinical and radiologic study. *J Oral Maxillofac Surg* 1991;**49**:585–93.
30. Moreno JC, Fernandez A, Ortiz JA, Montalvo JJ. Complication rates associated with different treatments for mandibular fractures. *J Oral Maxillofac Surg* 2000;**58**:273–80. discussion p. 80–1.
31. Assem FL, Levy LS. A review of current toxicological concerns on vanadium pentoxide and other vanadium compounds: gaps in knowledge and directions for future research. *J Toxicol Environ Health B Crit Rev* 2009;**12**:289–306.
32. O'Connell J, Murphy C, Ikeagwuani O, Adley C, Kearns G. The fate of titanium miniplates and screws used in maxillofacial surgery: a 10 year retrospective study. *Int J Oral Maxillofac Surg* 2009;**38**:731–5.

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ORIGINAL ARTICLE

Reconstruction of a fingertip with a thenar perforator island flap

SHINSUKE AKITA[1], TOMOAKI KUROKI[2], SHINYA YOSHIMOTO[1], NAOAKI RIKIHISA[1] & KANESHIGE SATOH[1]

[1]*Department of Plastic and Reconstructive Surgery, Chiba University Hospital, Chiba,* [2]*Department of Plastic and Reconstructive Surgery, Narita Redcross Hospital, Chiba, Japan*

Abstract

We raised thenar island flaps that were supplied by perforators that originated in the superficial palmar arch or the superficial palmar branch of the radial artery for the reconstruction of fingertip defects in eight patients. The flap was so well-vascularised that a large flap with increased mobility could be raised. The donor site was covered with well-vascularised thick tissue, and skin grafting of the donor site was avoided in all cases. No patient developed a complication, and all flaps survived. Functional and cosmetic results of both fingertips and donor sites were excellent. A perforator island flap from the thenar eminence can be raised easily without injuring any digital and palmar arteries. They have a good colour and texture that matches the fingertips and donor site defects on the palm.

Key Words: *Thenar flap, superficial palmar branch of the radial artery, superficial palmar arch, perforator flap*

Introduction

The glabrous skin of the palm provides the best tissue match for the reconstruction of defects of the volar hand and finger pulp. Only a few perforator flaps from the thenar eminence have been described [1,2]. Seyhan reported a perforator flap that was supplied with only a few perforators that originated in the superficial palmar arch or from the superficial palmar branch of the radial artery for the reconstruction of defects in the palm, first web, or proximal phalanx of the index finger [2].

We raised island flaps supplied by one to three perforators in eight patients when we used thenar flaps to reconstruct defects of the fingertips.

Patients and methods

From March 2008 to February 2009, eight patients (all men, mean age 33 years; range 23–39) (Table I) had fingertip defects reconstructed with thenar perforator flaps. Trauma was the cause of the defects in all patients. In five patients it was impossible to replant the amputated fingertip because of degloving injuries or severe crushing of amputated tissues. In one patient a replanted fingertip necrosed because of an arterial clot. Composite grafts necrosed in two patients.

The tip of the distal phalanx was exposed in all patients, but there was no significant loss of bone. The index finger was injured in five, the middle finger in two, and the ring finger in one patient. The right hand was involved in five patients.

Surgical technique

The superficial palmar branch of the radial artery is usually palpated over the tubercle of the scaphoid. Using Doppler ultrasound, cutaneous perforators can be identified preoperatively near a line drawn from the tubercle of the scaphoid to the intersection of the proximal palmar and thenar creases.

Based on the site of the pulse, the flaps can be designed in various forms (Figure 1). Although an

Correspondence: Shinsuke Akita, MD, Department of Plastic and Reconstructive Surgery, Chiba University Hospital, 1-8-1, Inohana, Chuo-ku, Chiba city, Chiba 260-8677, Japan. Tel: +81 43 226 2316. Fax: +81 43 226 2316. E-mail: shinsukeakita@graduate.chiba-u.jp

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Table I. Details of the patients.

Case No.	Age (years)	Sex	Cause of defect	Finger	Size of defect (mm)	Design	Sensation (mm) (2PD)
1	39	Male	Crush injury	L index	25 × 22	A	8
2	23	Male	Crush injury	R middle	17 × 13	A	5
3	38	Male	Necrosis after composite graft	R index	17 × 15	A	8
4	36	Male	Necrosis after replantation	R ring	30 × 22	C	10
5	31	Male	Degloving injury	R middle	35 × 22	C	4
6	31	Male	Degloving injury	R index	30 × 22	B	8
7	36	Male	Degloving injury	L index	35 × 22	C	5
8	21	Male	Necrosis after composite graft	L index	25 × 25	A	4

L = left, R = right. Design A = V-Y advancement flap based on a few perforators; design B = flap based on a single perforator is able to be rotated 180°; design C = bilobed island flap raised to cover the donor site defect of a skin-pedicled thenar flap.

advancement flap supplied by a few perforators is easier and safer to raise, it has lesser mobility (Figure 1A). Because a single perforator with a good pulse is enough for a flap, it is possible to raise a flap and rotate it 180° using the perforating point as a pivot (Figure 1B). In both designs A and B, the flap should be large enough to cover not only the fingertip defect but also the donor site defect using its own proximal side. It is also possible to reconstruct the fingertip defect with a thenar flap pedicled on skin and design a bilobed island flap supplied by a perforator on the thenar eminence to cover the donor site defect (Figure 1C).

The operation is done under nerve block anaesthesia and pneumatic tourniquet control without exsanguinating the upper extremity.

A cutaneous incision is made along the outline of the flap, and the subcutaneous layer is dissected to avoid neurovascular injury. After the perforators have been identified, there is no need to identify the main arteries feeding them or to dissect the perforators into the muscle. Although the fascia around the perforator is raised with the flap to avoid needless vascular injury, it is not necessary for nourishment of the flap. The superficial palmar branch of the radial artery, palmar digital nerves, and motor branch of the median nerve, which run under the fascia, are preserved.

After the flap has been raised, the tourniquet is released and circulation of the flap confirmed. The raised flap is transposed and sutured to the fingertip defect or the donor site.

The operated hand is kept raised for several days after the operation. The flap is divided within two weeks after the first operation, and active and passive exercises for the finger are begun immediately.

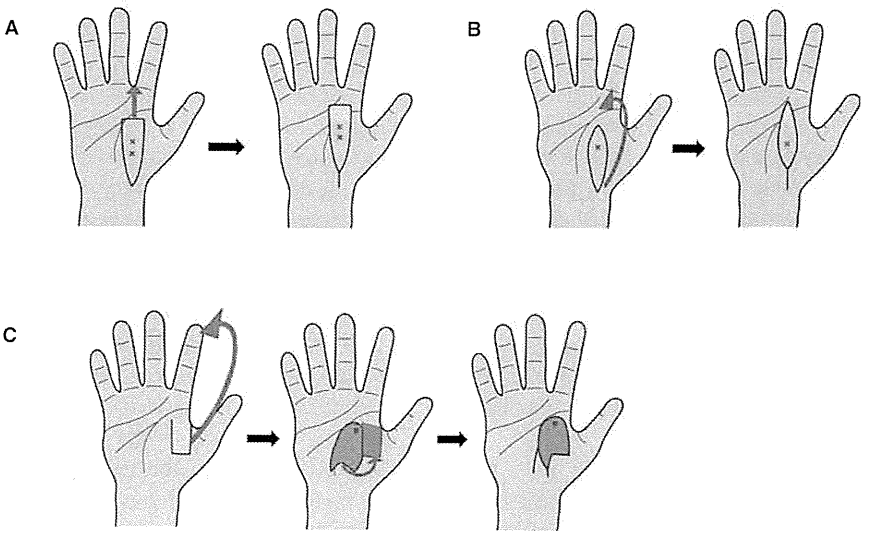

Figure 1. Three designs for covering the defects. Design A = V-Y advancement flap based on a few perforators. Design B = Flap based on a single perforator is able to be rotated 180°. Design C = Bilobed island flap is elevated to cover the donor site defect of a skin-pedicled thenar flap.

Both reconstructed fingertip and donor site were evaluated for pain, intolerance to cold, range of movement, and aesthetic appearance including matching of colour and texture. Assessment of the sensory restoration of the fingertip was made based on two-point discrimination test using the method described by Moberg [3].

Results

The perforator flap was rotated 180° in one patient, advanced in V-Y fashion in four, and raised as a bilobed island flap in three. The flap included one to three perforators (mean 2.0). The flap could be advanced up to 25 mm as a V–Y advancement flap (case 5). The largest flaps were 55 × 30 mm (case 6) and 65 × 25 mm (case 7).

All flaps survived completely, and there were no intraoperative and postoperative complications such as nerve injuries, wound dehiscence, or wound infections. The mean follow-up was 8 months (range 6–9).

All flaps of both fingertips and thenar eminences had excellent matching of colour and texture. The cosmetic results of all thenar eminence flaps were noted to be satisfactory without shrinkage. No patient complained of pain at the donor site or reconstructed fingertip, and no joint contracture or cold intolerance was reported. The mean two point discrimination was 6.5 mm (range 4–10).

Case reports

Case 1. The thenar perforator flap was transposed as a V–Y advancement flap. A 39-year-old man sustained an avulsion injury to his right index finger with traumatic amputation of the fingertip by a machine. The fingertip defect to be reconstructed was 25 × 25 mm (Figure 2*a*). A 65 × 25 mm flap supplied by three perforators, all of which originated in the superficial palmar branch of the radial artery, was raised and advanced 25 mm distally (Figure 2*b*). The index fingertip was reconstructed with the distal side of the flap, and the donor site of the flap was covered by the proximal side of the flap with a V–Y advancement procedure (Figure 2*c*).

The flap was divided 14 days after the first operation. The postoperative course was uneventful, and the functional and cosmetic results were excellent (Figure 2*d*).

Case 6. A thenar perforator flap was rotated 180° and the fingertip was reconstructed with its distal side. A 31-year-old man sustained an avulsion injury to his right index finger with traumatic amputation of the fingertip by a machine. The fingertip defect to be reconstructed was 30 × 22 mm (Figure 3*a*). A 65 × 22 mm flap supplied by a perforator was raised and rotated 180° (Figure 3*b*, *c*). The index fingertip was reconstructed with the distal side of the flap, which formed a triangle with a base of 22 mm and a height of 35 mm. The donor site for this flap was covered with the proximal side of the flap. The raised flap was so long that the metacarpophalangeal and interphalangeal joints of the index finger were allowed to be in lesser degrees of flexion postoperatively (Figure 3*d*). The flap was divided 14 days after the first operation. The postoperative course was uneventful, and the functional and cosmetic results were excellent (Figure 3*e*).

Case 7. A thenar perforator flap was raised as a bilobed island flap to cover the donor site defect of a thenar flap. A 36-year-old man sustained an avulsion injury to his left index finger with traumatic amputation of the fingertip. The fingertip defect that had to be reconstructed was 35 × 22 mm (Figure 4*a*). A distally-based thenar flap with a skin pedicle was designed to reconstruct the fingertip. A 55 × 30 mm bilobed flap supplied by two perforators was also designed to its ulnar side to cover the donor site defect (Figure 4*b*). The two flaps were raised and sutured at the same time (Figure 4*c*, *d*). The thenar flap was divided 12 days after the first operation. The postoperative course was uneventful, and the functional and cosmetic results were excellent (Figure 4*e*).

Discussion

The thenar and midpalmar areas are supplied by perforators that originate in the superficial palmar arch, the deep palmar arch, and the superficial palmar branch of the radial artery. In particular, the proximal area of the thenar eminence is supplied mainly by perforators that originate in the superficial palmar branch of the radial artery.

Omokawa et al. [4] examined 30 fresh-frozen cadaver hands and reported on the vascular anatomy of the thenar area. The superficial palmar branch of the radial artery usually bifurcated ulnarly from the main trunk of the radial artery about 1–2 cm proximal to the distal crease of the wrist, and ran distally beneath the flexor retinaculum of the wrist as it passed over the tuberosity of the scaphoid. After providing a nutrient branch to the thenar muscle, it ran through the thenar fascia and consistently provided 1–5 perforating branches.

Although there are dense connections between the terminal branch of the superficial palmar arch, superficial palmar branch of the radial artery, princeps

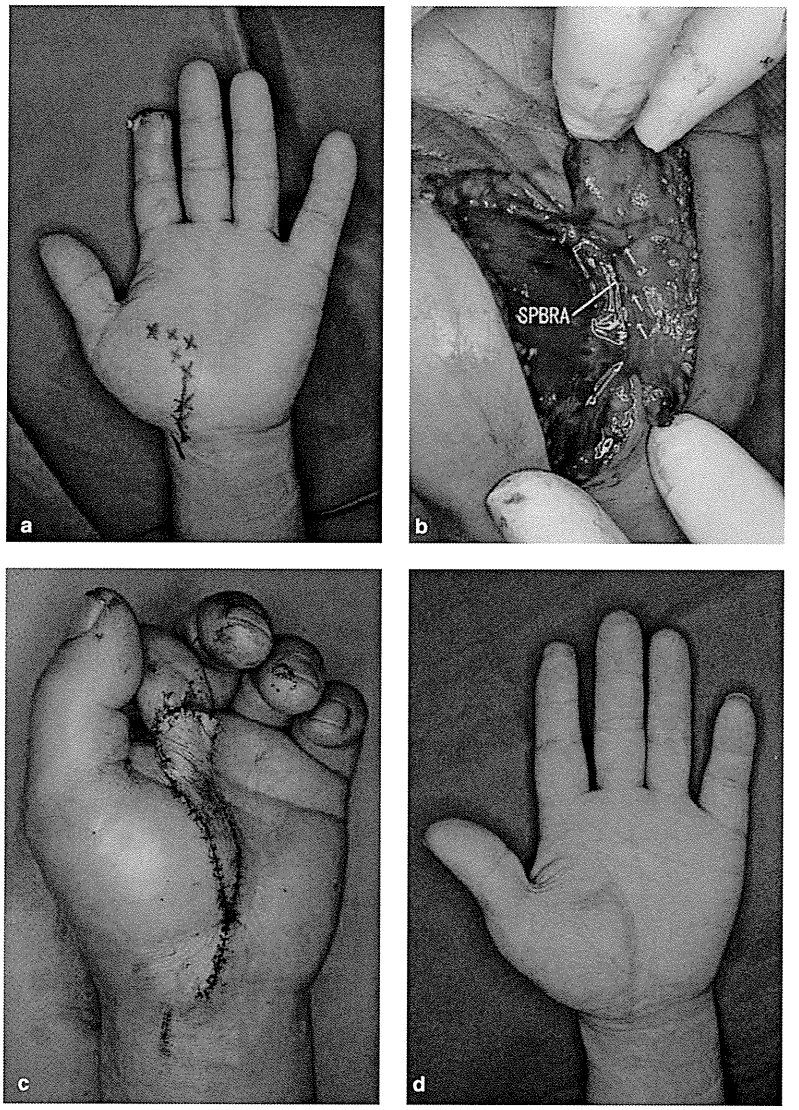

Figure 2. (*a*) A 39-year-old man with a defect of the right index finger. The site of the pulse sound is marked. (*b*) The arrows show the perforators. SPBRA = superficial palmar branch of the radial artery. (*c*) Immediately after the operation. (*d*) Six months after the operation.

pollicis artery, and deep palmar arch around the intersection of the proximal palmar and thenar crease, Omokawa et al. [4] reported that there was a connection between the superficial palmar branch of the radial artery and other arteries in only 63% of 30 hands dissected. In another study, Omokawa et al. [5] reported that there was a connection between the superficial palmar arch and the radialis indicis artery in 42%, and between the superficial palmar arch and the princeps pollicis artery in 85% of 24 specimens dissected. These results indicated that it is not always possible to transport a flap from the thenar eminence distally as a reverse-flow island flap. Although several authors have reported a free or reversed flap with an axial circulation pattern from the glabrous skin of the thenar eminence [6–10], only a few perforator flaps have been described [1,2]. Seyhan [2] reported that only one or two perforators with a good pulse were enough to nourish a thenar eminence flap, and he reconstructed a defect in the palm or the first web space without dissecting the main arteries that feed the perforators. Operating time can be shortened and the risk of complications such as nerve injury can be decreased if the main trunk of the artery is not dissected.

Although it is a two-stage technique, the thenar flap is a useful way to reconstruct fingertip injuries because it can restore the bulk and contour of the finger pulp with its plentiful subcutaneous tissue. When the initial injury does not involve either a tendon or an interphalangeal joint, patients regain normal movement of the finger within two weeks of division of the pedicle.

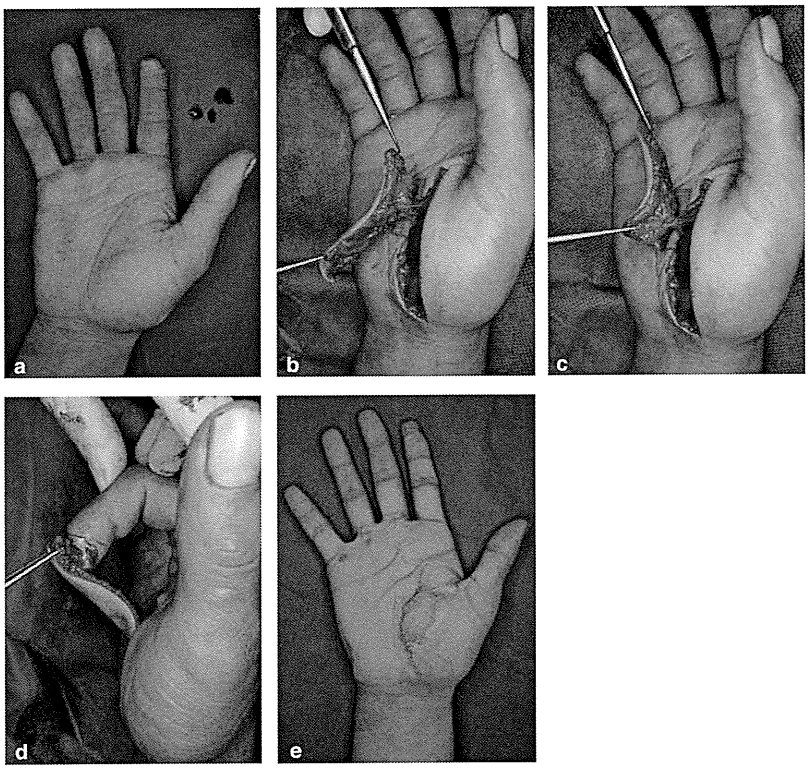

Figure 3. (*a*) A 31-year-old man with a defect of the right index finger. (*b*, *c*) A flap 65 × 22 mm was raised and rotated. (*d*) The metacarpophalangeal and interphalangeal joints were allowed to be in lesser degrees of flexion postoperatively. (*e*) Five months after the operation.

There is also a low complication rate, the procedure does not injure proper digital nerves, and recovery of the sensitivity is relatively good. In our series, the patients obtained exceptionally good sensation in the reconstructed fingertips; although we could not find a definite reason, one may be that all our patients were less than 40-years-old. Kleinert et al. [11] reported good sensory return with a non-innervated flap for coverage of the finger defect, and the sensory return seemed better in younger patients.

The donor site of the thenar flap has been closed directly or covered by a skin graft. Dellon [12] reported that the donor sites up to 15 mm could be closed directly without contracture. However, Nomura et al. [13] suggested that most donor site defects are wider. They reported that repair with a split-thickness skin graft from the hypothenar eminence is better because it matches colour and texture well.

However, the subcutaneous layer of fat on the thenar eminence cannot be reconstructed with a skin graft, and the grafted skin may shrink and contract the thenar eminence. In addition, if the grafted skin becomes unstable, rehabilitation of the hand will be delayed. A skin graft may also require the sacrifice of other donor sites such as the hypothenar eminence, plantar pedis, or other places, and offers poorer colour and texture matching.

From these points of view, reconstruction using a flap adjacent to the defect is considered to be a better option because the best colour and texture matching can be obtained, and subcutaneous tissue can be reconstructed with minimum sacrifice of healthy skin.

We reconstructed index, middle, and ring fingertips using thenar island flaps supplied by one to three perforators. Because flap circulation was stable, the flap resulted in good mobility, and we could raise a large flap from the proximal area of the thenar eminence and cover both the fingertip and the donor site defects at the same time. Both the reconstructed fingertip and thenar eminence obtained the best colour and texture matching and thickness of subcutaneous tissue.

By transposing the flap at the time of the first operation, its circulation becomes more stable before the second operation. Patients can be started on aggressive rehabilitation immediately after the second operation. Because a long flap could be raised, the finger joints were allowed to be in lesser degrees of flexion until the second operation, which might help prevent contractures.

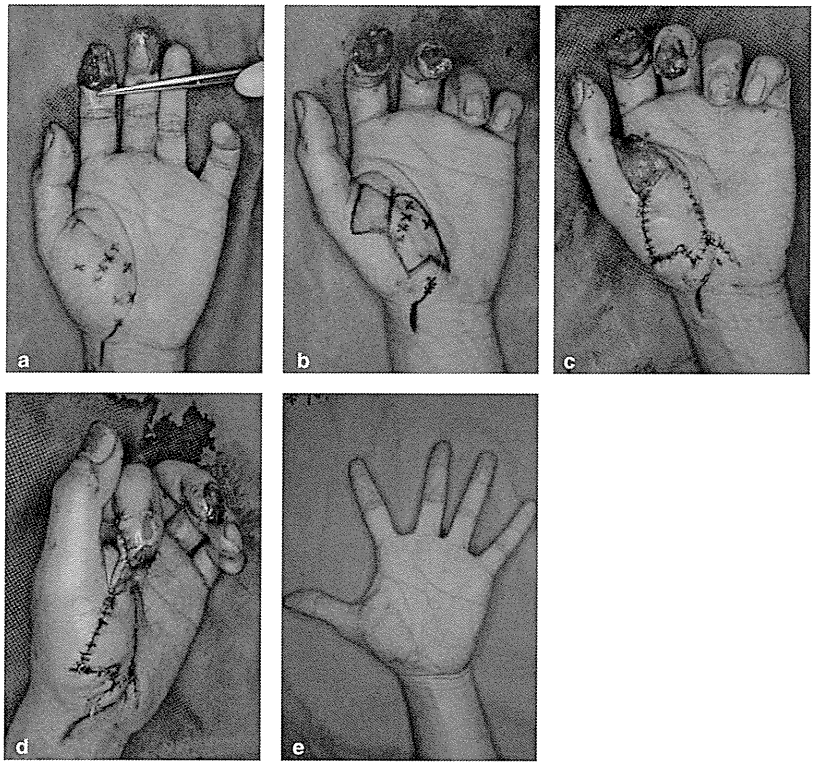

Figure 4. (*a*) A 36-year-old man with a defect of the left index finger. The site of the pulse sound is marked. (*b*) A skin-pedicled thenar flap and a bilobed island flap. (*c*, *d*) The two flaps were raised and sutured at the same time. (*e*) Six months after the operation.

The thenar flap becomes better vascularised and develops better mobility by being raised as a perforator flap, and the donor site defect can be covered without using a skin graft.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Vasconez LO, Velasquez CA, Rumley T. Correction of a first web space contracture with an arterialized palmar flap. In: Gilbert A, Masquelet AC, Hentz RV, editors. Pedicle flaps of the upper limb. Boston: Little Brown; 1992. p 135–8.

[2] Seyhan T. Reverse thenar perforator flap for volar hand reconstruction. J Plast Reconstr Aesthet Surg 2009;62:1309–16.

[3] Moberg E. Two-point discrimination test. A valuable part of hand surgical rehabilitation, e.g. in tetraplegia. Scand J Rehabil Med 1990;22:127–34.

[4] Omokawa S, Ryu J, Tang JB, Han JS. Vascular and neural anatomy of the thenar area of the hand: its surgical applications. Plast Reconstr Surg 1997;99:116–21.

[5] Omokawa S, Tanaka Y, Ryu J, Clovis N. Anatomical consideration of reverse-flow island flap transfers from the midpalm for finger reconstruction. Plast Reconstr Surg 2001; 108:2020–5.

[6] Kamei K, Ide Y, Kimura T. A new free thenar flap. Plast Reconstr Surg 1993;92:1380–4.

[7] Kamei K, Shimada K, Kimura T, Ueno T. Substantial volar defects of the fingers treated with free thenar flaps. Scand J Plast Reconstr Surg Hand Surg 1997;31:87–90.

[8] Omokawa S, Mizumoto S, Iwai M, Tamai S, Fukui A. Innervated radial thenar flap for sensory reconstruction of fingers. J Hand Surg 1996;21A:373–80.

[9] Omokawa S, Takaoka T, Shigematsu K, et al. Reverse-flow island flap from the thenar area of the hand. J Reconstr Microsurg 2002;18:659–64.

[10] Sassu P, Lin CH, Lin YT, Lin CH. Fourteen cases of free thenar flap: a rare indication in digital reconstruction. Ann Plast Surg 2008;60:260–6.

[11] Kleinert HE, McAlister CG, MacDonald CJ, Kutz JE. A critical evaluation of cross finger flaps. J Trauma 1974; 14:756–63.

[12] Dellon AL. The proximal inset thenar flap for finger-tip reconstruction. Plast Reconstr Surg 1983;72:698–704.

[13] Nomura S, Kurakata M, Sekiya S. The modified thenar flap method and its usefulness. J Jpn Soc Surg Hand 2000;16: 707–11. [in Japanese]

EXPERT REVIEWS

Efficacy and safety of pitavastatin in Japanese patients with hypercholesterolemia: LIVES study and subanalysis

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Koutaro Yokote[†1], Hitoshi Shimano[2], Mitsuyoshi Urashima[3] and Tamio Teramoto[4]

[1]*Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan*
[2]*Department of Internal Medicine, Metabolism and Endocrinology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan*
[3]*Division of Molecular Epidemiology, Jikei University School of Medicine, Tokyo, Japan*
[4]*Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan*
[†]*Author for correspondence: kyokote@faculty.chiba-u.jp*

The Livalo Effectiveness and Safety (LIVES) study was an observational study to examine the efficacy and safety of pitavastatin, a newly developed drug, in approximately 20,000 Japanese patients with hypercholesterolemia. During a 2-year follow-up period, no significant problems concerning safety were observed upon treatment with pitavastatin. Pitavastatin demonstrated potent and stable lowering of the LDL-cholesterol level. The LIVES study subanalyses revealed significant and continuous elevation of HDL-cholesterol in association with pitavastatin treatment and also showed that the drug did not adversely affect glycemic control as evaluated by the glycohemoglobin A_{1c} level. Moreover, pitavastatin treatment was associated with an increase in estimated glomerular filtration rate in subjects with chronic kidney disease. These results suggest the usefulness of pitavastatin in hypercholesterolemic patients from various backgrounds. The ongoing LIVES study extension is expected to provide further data on cardiovascular outcome in subjects treated with pitavastatin.

KEYWORDS: CKD • efficacy • eGFR • HbA_{1c} • HDL-C • LDL-C • pitavastatin • safety

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the most effective drugs for lowering LDL-cholesterol (LDL-C) and are used as a first choice for the treatment of hypercholesterolemia. A number of clinical trials have demonstrated their efficacy in both primary and secondary prevention of cardiovascular disease (CVD) [1–3].

Pitavastatin (Livalo® tablet) is a synthetic statin developed by Nissan Chemical Industries, Ltd (Tokyo, Japan) and Kowa Company, Ltd (Tokyo, Japan). The basic characteristics, clinical efficacy and safety of pitavastatin have been reviewed by Teramoto *et al.* [4]. Phase II and III clinical trials in Japan demonstrated that pitavastatin has potent activity in lowering serum LDL-C, total cholesterol (TC) and triglyceride (TG) levels, and elevating HDL-cholesterol (HDL-C) levels. The incidence and pattern of adverse reactions caused by pitavastatin and other statins currently in use were not significantly different [5–10]. On the basis of these results, manufacturing approval was granted for pitavastatin to be launched in the Japanese market in September 2003. Thereafter, the drug has been launched in overseas markets, including Korea (July 2005), Thailand (January 2008), China (July 2009) and the USA (June 2010), and was also approved for marketing in Europe in July 2010.

The Livalo Effectiveness and Safety (LIVES) study is a large-scale, long-term, prospective post-marketing surveillance study [11]. This observational study was designed with the following main objectives:

- To identify any previously unknown adverse reactions/events;
- Evaluate the incidence and pattern of adverse reactions under actual use conditions;
- Identify clinical factors that might affect the safety and effectiveness of the drug.

Large amounts of data have been collected during the 2 years of observation and have been subjected to three subanalyses on the efficacy and safety of pitavastatin [4,12,13].

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Table 1. Patient demographic characteristics.

Items			Patients (n)	%
Gender	Male		6646	32.8
	Female		13,633	67.2
Age	<65 years		10,532	51.9
	≤65 years		9747	48.1
	<75 years		17,027	84
	≤75 years		3252	16
	Mean ± SD: 63.3 ± 11.3			
Comorbid conditions	Hypertension		9510	46.9
	Diabetes mellitus		5174	25.5
	Heart disease		2947	14.5
	Liver disease		1606	7.9
	Renal disease		721	3.6
	Cataract		511	2.5
	Arteriosclerosis obliterans		338	1.7
Patient category†	Primary prevention	I (low-risk group)	1224	6
		II (intermediate-risk group)	10,990	54.2
		III (high-risk group)	6258	30.9
	Secondary prevention		1489	7.3
Previous hyperlipidemia medication	No		16,442	81.1
	Yes		3837	18.9
Initial daily dose	1 mg		8002	39.5
	2 mg		12,164	60
	4 mg		74	0.4
Most frequent daily dose	1 mg		8124	40.1
	2 mg		11,844	58.4
	4 mg		186	0.9

Category I, II, and III are primary prevention.
Concerning the number of major risk factors other than LDL-cholesterol for each category, I is 0, II is 1–2, and III is 3 or more.
Major risk factors other than LDL-cholesterol are as follows: aging (male ≥45 years, female ≥55 years), hypertension, diabetes (including impaired glucose tolerance), smoking, family history of coronary artery disease and low HDL-cholesterol (<40 mg/dl).
†Japan Atherosclerosis Society (JAS) guidelines for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese.
SD: Standard deviation.
Adapted with permission from [11].

Survey participants

In this study, 20,279 subjects with hypercholesterolemia, including familial hypercholesterolemia (n = 318; 1.6%), were enrolled within 14 days after the initiation of pitavastatin during the registration period between December 2003 and March 2005. Completion of a 2-year follow-up was carried out by the end of March 2007. Among all participants, 19,925 individuals were subjected to the safety analysis, and 18,031 individuals were analyzed for the drug's efficacy. Demographic characteristics of the subjects are shown in Table 1. The mean age of the participants was 63.3 ± 11.3 years. The major comorbid conditions of participants included hypertension, diabetes mellitus and heart disease. A total of 1489 had a history of coronary artery disease. The subjects without a history of coronary artery disease were classified into risk groups for primary prevention. In accordance with the Japan Atherosclerosis Society (JAS) guidelines for diagnosis and prevention of atherosclerotic cardiovascular diseases [14], 30.9% were classified into a high-risk group (category III) and 54.2% into an intermediate-risk group (category II) of primary prevention. Among all study subjects, 18.9% had a history of taking any lipid-lowering medication before entering the study. The initial daily dose of pitavastatin was 1 mg for 39.5% of the subjects and 2 mg for 60% of them. The LIVES study was a postmarketing surveillance study, and the demographic characteristics were different from the entire Japanese hypercholesterolemia population.

Incidence of adverse drug reactions

As shown in Table 2, the incidence of adverse drug reactions were reported during 12 weeks (6.1%), 1 year (8.8%), and 2 years (10.4%) of observation. The major adverse drug reactions at 2 years were an elevation of serum creatine phosphokinase (2.74%), alanine aminotransferase (1.79%), aspartate aminotransferase (1.5%), and γ-glutamyltransferase (γ-GP; 1%), as well as myalgia (1.08%). The determination of enzyme elevation was evaluated by primary physicians. Most of the adverse drug reactions were mild in severity (mild in 1735 patients, moderate in 307 patients, and serious in 27 patients), and no previously unknown adverse drug reactions were observed. A single case of serious rhabdomyolysis was reported (one out of 19,925 individuals; 0.005%). The subject, a male in his 40s, developed rhabdomyolysis 411 days after initiation of pitavastatin 1 mg, and the symptom resolved without any disability after discontinuation of the drug.

Factorial analysis of adverse drug reactions

The relationship between the rate of adverse drug reactions and various factors was analyzed (Table 3). The incidence of adverse drug reactions differed significantly, depending on the presence or absence of drug allergy, concomitant liver disease, renal disease, diabetes mellitus or hypertension. Subject age of 75 years and older did not affect the incidence of adverse reactions.

Table 2. Incidence of adverse drug reactions.

Term of surveillance (weeks)	104
Incidence rate of adverse drug reactions (%)	10.4
Patients with adverse drug reactions/ total patients evaluated (n)	2069/19,925
Patients with serious adverse drug reactions (n)	27
Type of serious drug adverse reactions	*Cumulative number of patients*
Diabetes mellitus	1
Cerebral hemorrhage	1
Cerebral infarction	1
Loss of consciousness	1
Syncope	1
Cataract operation	3
Coronary artery disease	1
Diarrhea	1
Liver disorder	3
Abnormal hepatic function	3
Cholestatic jaundice	1
Rhabdomyolysis	1
Muscular weakness	1
Blood CK, increased malaise	1
Nephrotic syndrome	1
Nephritis interstitial	1
Interstitial lung disease	1
Drug eruption	1
AST, ALT and LDH increased	1
AST and ALT increased	1

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine phosphokinase; LDH: Lactate dehydrogenase.
Adapted with permission from [11].

Clinical factors analysis

The main purpose of the LIVES study was to evaluate the efficacy of pitavastatin, examine the incidence and pattern of adverse reactions, and detect any previously unknown side effects. In addition, *post hoc* analyses were performed using the LIVES study database to examine the change in lipid profile, glycohemoglobin A_{1c} (HbA_{1c}) in diabetes mellitus, and estimated glomerular filtration rate (eGFR) in chronic kidney disease (CKD; Table 4) [4,12,13].

Effects on lipid profile

The lipid changes were analyzed in patients whose efficacy data were eligible at 104 weeks. Percentage change in TC, LDL-C, TG (all subjects including the high TG subgroup [≥150 mg/dl at baseline]), HDL-C (all subjects including the low HDL-C subgroup [<40 mg/dl at baseline]) and non-HDL-C were calculated (Table 4A). LDL-C level was estimated using the Friedewald formula (LDL-C = TC - HDL-C - TG × 0.2) in patients with TG less than 400 mg/dl [15]. If the Friedwald formula could not be used, a direct LDL-C measurement method was used.

A significant reduction in TC (-21.0%), LDL-C (-31.3%) and non-HDL-C (-28.5%) was observed at 104 weeks. The percentage reduction in TG was 6.1% for the whole population and 24.2% in the high TG subgroup. The percentage increase in HDL-C was 5.9% for the whole population and 24.6% in the low HDL-C subgroup. The long-term efficacy of pitavastatin was analyzed in subjects whose lipid data were available at 0, 12, 28, 52 and 104 weeks. The results showed that pitavastatin significantly and stably reduced serum LDL-C (Figure 1A).

Interestingly, serum HDL-C gradually increased throughout the observation period in a continuous manner (Figure 1B). To be noted, HDL-C increased by 24.6% from 35.1 to 43.3 mg/dl on average in the low HDL-C subgroup, and all the subjects achieved the treatment goal of 40 mg/dl or higher for HDL-C, as recommended by the JAS guidelines [14]. Significant increase in HDL-C was also observed in the subjects who had been taking cholesterol-lowering drugs other than pitavastatin (+15.8%; $p < 0.001$). The patients' baseline characters, complications, other pretreated lipid-lowering drugs and dose of pitavastatin were entered into a multivariate regression model to reveal the factors affecting the change of HDL-C. Multivariate analysis showed that high BMI, the presence of diabetes mellitus or liver disease, and change from other cholesterol-lowering drugs were significant factors that negatively affected the increase in HDL-C.

A similar change in lipids, that is, significant reduction in TC, LDL-C, TG in the high TG subgroup, and non-HDL-C was observed in patients with CKD (baseline eGFR <60 min/ml/1.73 m^2; Table 4B) or with diabetes mellitus (Table 4C).

Effect on eGFR

Several studies have addressed the potential benefits of statins in improving renal function, such as reduction of albuminuria and elevation of eGFR [16,17]. However, there were also reports of detrimental effects on renal function [18–21]. In order to evaluate the effect of pitavastatin treatment on renal function, eGFR was assessed in the LIVES study, using the Japanese revised equation, as follows: eGFR (ml/min/1.73 m^2) = 194 × Cr - 1.094 × age - 0.287 (×0.739, if female) [22]. Baseline eGFR values <60 ml/min/1.73 m^2 (n = 958) were defined as CKD, and patients with these eGFR values were enrolled for the subanalysis.

A significant increase in eGFR (+5.4) was observed after 104 weeks of pitavastatin treatment (Table 4B). Time-course analysis showed that in patients whose eGFR data were available for all 0-, 12-, 28-, 52- and 104-week time points, eGFR was elevated by 2.4 and 5.6 ml/min/1.73 m^2 after 14 and 104 weeks of treatment, respectively (Figure 1C). The patients' baseline characters, complications, presence/absence of proteinuria, other pretreated lipid-lowering drugs, dose of pitavastatin, and the amount of change of serum lipids were entered into a multivariate regression model to reveal the factors affecting the change of eGFR. Multivariate analysis showed that the absence of proteinuria at

Table 3. Factorial analysis of adverse drug reactions.

Items		Incidence rate (%)	Patients with incidences/ total number of patients	p-value†
Gender	Male	10.9	713/6535	0.089
	Female	10.1	1356/13,390	
Age (years)	<65	10.0	1029/10,311	0.053
	≤65	10.8	1040/9614	
	<75	10.5	1747/16,706	0.437
	≤75	10.0	322/3219	
Daily dosage upon first onset	1 mg	11.0	879/7989	0.016‡
	2 mg	10.0	1168/11,635	
	4 mg	7.7	14/181	
Drug allergy	No	10.3	1976/19,387	<0.001
	Yes	20.4	97/476	
Liver disease	No	10.1	1855/18,343	<0.001
	Yes	13.5	214/1580	
Renal disease	No	10.3	1971/19,203	0.004
	Yes	13.6	98/720	
Diabetes mellitus	No	10.1	1492/14,790	0.020
	Yes	11.2	577/5133	
Hypertension	No	10.0	1047/10,487	0.050
	Yes	10.8	1022/9436	
Comorbid conditions or history of heart disease	No	10.3	1710/16,669	0.189
	Yes	11.0	359/3256	

†Square test.
‡Cochrane–Armitage test.
Adapted with permission from [11].

the baseline and the increase in HDL-C level during the study period were clinical factors that positively influenced eGFR upon pitavastatin treatment.

Influence on HbA_{1c}

The influence of pitavastatin on HbA_{1c} in patients with diabetes mellitus was also evaluated. Among the patients subjected to the analysis, 1197 were hypercholesterolemic patients with diabetes mellitus whose HbA_{1c} data were available both at baseline and at 104 weeks. A significant decrease in HbA_{1c} was observed after 104 weeks of pitavastatin treatment, under the condition where change in antidiabetic therapy was allowed. The changes in HbA_{1c} were +0.077% (6.25–6.22%; p = 0.13; n = 205) in patients without antidiabetes mellitus therapy at baseline and -0.28% (7.51–7.23%; p < 0.001; n = 922) in patients with antidiabetes mellitus therapy at baseline. In the time-course analysis, HbA_{1c} gradually, decreased by 0.28% over the 104 weeks (Figure 1D). The patients' baseline characters, complications, presence/absence of previous use of lipid-lowering drugs and antidiabetes mellitus therapy, dose of pitavastatin, and the percentage change of serum lipids were entered into multivariate regression model to reveal the factors affected during the change of HbA_{1c}. The multivariate analysis identified the presence/absence of antidiabetes mellitus therapy and percentage changes in LDL-C and TG as clinical factors influencing the decrease in HbA_{1c} induced by pitavastatin treatment. According to the LIVES subanalysis, pitavastatin did not adversely affect glucose metabolism.

Expert commentary

The LIVES study was initiated as a large-scale, long-term, prospective postmarketing surveillance and provided large amounts of safety data of approximately 20,000 patients for 2 years. The number of patients was designed to enable detection of unknown adverse drug reactions that could develop at an incidence of 0.05% or higher and at a probability of over 99%. This study showed a low incidence of adverse events with pitavastatin during 104 weeks and confirmed a reliable safety profile for the drug. Moreover, pitavastatin was shown to have a potent activity in lowering TC, LDL-C and non-HDL-C.

The results of the LIVES study subanalyses further revealed some unique properties of pitavastatin. For example, it was shown that pitavastatin not only has a potent and stable lowering effect on LDL-C, but also continuously increases HDL-C, as observed during 2 years follow-up. These findings are consistent with and support the effect of pitavastatin on increasing HDL-C which was shown in a previous study. The study was conducted to compare the effects of pitavastatin (2 mg/day) and atorvastatin (10 mg/day) on HDL-C levels in hypercholesterolemic patients with glucose intolerance (n = 173) [23]. Percentage change in HDL-C during 52 weeks, the primary end point of the study, was significantly higher in the pitavastatin group (8.8%), compared with that in the atorvastatin group (3.6%; p = 0.031 vs pitavastatin group). The results of the comparative study and LIVES study suggest that pitavastatin is a suitable agent for the management of both LDL-C and HDL-C, two major lipid risk factors for CVD. The ability of pitavastatin to elevate HDL-C may be related to its effect on increasing hepatic apolipoprotein A-I production [24], but the precise mechanism remains to be elucidated.

In addition to being a significant risk factor for progression to end-stage renal disease, CKD is established as a risk factor for developing CVD [25,26]. The result of a recent meta-analysis demonstrated that a low eGFR value was negatively related to all-cause mortality and cardiovascular mortality [27]. In the LIVES study subanalysis on 958 patients with eGFR <60 ml/min/1.73 m^2, treatment with pitavastatin was associated with a significant increase in eGFR during the 2 years of follow-up [13]. Interestingly, the results of a multivariate analysis suggest that the effect of pitavastatin on

Table 4. Change in the clinical factors of each background.

Items (mg/dl)	Lipid value								
	A: All patients			*B: Patients with eGFR <60 ml/min/1.73 m²*			*C: Patients with diabetes mellitus*		
	Patients (n)	*Baseline 104 weeks*	*Change from baseline (%)*	*Patients (n)*	*Baseline 104 weeks*	*Change from baseline (%)*	*Patients (n)*	*Baseline 104 weeks*	*Change from baseline (%)*
TC	4084	254.1 ± 37.6 197.7 ± 33.2	-21 ± 15*	914	254.0 ± 41.6 193.4 ± 34.3	-22.5 ± 15.5*	1028	249.0 ± 41.3 194.2 ± 35.0	-20.7 ± 15.8*
LDL-C	1455	165.2 ± 35.5 110.3 ± 28.0	-31.3 ± 26*	341	165.7 ± 37.4 109.0 ± 28.5	-31.3 ± 24.1*	336	159.4 ± 36.2 107.0 ± 27.5	-30.2 ± 21.0*
TG	4123	179.9 ± 127.6 146.1 ± 94.9	-6.1 ± 50.0*	903	186.8 ± 126.7 152.1 ± 88.2	-6.4 ± 50.6**	1095	194.4 ± 140.2 155.2 ± 120.5	-8.2 ± 52.0*
TG (baseline value ≥150 mg/dl)	2088	254.9 ± 141.5 179.8 ± 112.4	-24.2 ± 37.6*	494	253.3 ± 137.7 182.5 ± 98.3	-21.8 ± 38.1*	621	263.3 ± 152.2 186.3 ± 141.6	-23.7 ± 39.9*
HDL-C	3427	58.8 ± 17.1 60.8 ± 15.9	5.9 ± 21.5*	739	56.8 ± 16.7 59.2 ± 16.0	6.6 ± 20.5*	912	55.9 ± 15.6 57.9 ± 15.1	5.8 ± 20.1*
HDL-C (baseline value <40 mg/dl)	346	35.1 ± 3.6 43.3 ± 9.8	24.6 ± 34.7*	91	34.7 ± 4.0 41.9 ± 7.7	21.5 ± 22.3*	116	35.2 ± 3.4 42.1 ± 8.0	20.5 ± 27.5*
Non-HDL-C	3260	195.3 ± 38.9 136.8 ± 33.1	-28.5 ± 29.8*	714	197.6 ± 42.7 133.8 ± 32.9	-30.2 ± 19.5*	832	191.9 ± 42.5 135.0 ± 34.3	-27.2 ± 20.9*
					eGFR (ml/min/1.73 m²)	*Change value from baseline*		*HbA_{1c} (%)*	*Change value from baseline*
				958	47.8 ± 11.5 53.2 ± 18.6	5.4 ± 13.3**	1197	7.28 ± 1.51 7.06 ± 1.35	-0.22 ± 1.37**

*p < 0.0001.
**p < 0.001.
One-sample t-test.
Mean ± SD.
eGFR: Estimated glomerular filtration rate; HbA_{1c}: Glycohemoglobin A_{1c}; HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol; TC: Total cholesterol; TG: Triglyceride.
Adapted in part with permission from [12,13].