Nonmicrosurgical options for soft tissue reconstruction of the hand

Jun Matsui · Samantha Piper · Martin I. Boyer

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Abstract There are many options for nonmicrosurgical soft tissue coverage of hand wounds, ranging from split thickness skin grafting to pedicled soft tissue transfer, depending on the size, location, blood supply, and depth of the wound. Although many of these techniques have been available for decades, recent advancements in wound management include synthetic dermal substitution, new dressing materials, and variations on previously described or novel pedicled flaps.

The goals of coverage include maximizing healing, function, aesthetic appearance, and patient satisfaction, while minimizing donor site morbidity. Optimal management often relies on an individual surgeon's assessment and judgment, as hand wounds can vary greatly and pose unique challenges, and multiple coverage options often exist for each wound. Here, we aim to present useful and up-to-date information on nonmicrosurgical soft tissue coverage for hand reconstruction focusing on recent findings of interest to provide an update on areas with evolving evidence.

Keywords Soft tissue · Coverage · Hand wounds · Skin graft · Dermal substitute · Fingertip injury · Thumb injury · Negative pressure wound therapy

Introduction

Skin and soft tissue defects are common in the hand, often in the setting of open fracture, trauma, or infection. Nonmicrosurgical options fall into the middle of the reconstructive ladder, between primary closure and distant or free flaps. These coverage options tend to be more robust than free

tissue transfer, but require careful planning and decision-making to choose the most appropriate coverage while remaining aware of potential complications and future management options.

Due to the wide range of wounds in the hand, the surgeon must use the best evidence available to make informed and deliberate decisions about the best coverage for the wound. The vascularity of the wound bed, location on the hand, and desired function all influence determination of the optimal coverage, as well as the need for sensation, aesthetics, and minimizing donor site morbidity. This review will discuss recent advances in options for nonmicrosurgical soft tissue coverage of hand wounds.

Skin grafts

Transferring skin from one part to another, either full thickness (epidermis and dermis) or partial thickness (epidermis alone) provides a simple, technically straightforward option when the wound depth is relatively shallow and exposed structures are amenable to healing to the transferred skin.

Split thickness skin graft (STSG)

The split thickness skin graft is insensate and can be meshed, allowing for coverage of a larger surface area as well as draining of postoperative hematoma. Healing occurs through epithelialization from the hair follicles, and depends on a properly vascularized bed for healing. Grafts will most reliably adhere to fascia, paratenon, and muscle. Some amount of tissue contraction occurs with healing, so the recipient site should be one that will not be debilitated by wound contraction. Thicker split thickness skin grafts contract less due to having more dermis. Complications include postoperative hematoma or seroma, which can detach the graft from the underlying wound bed, making the graft nonviable. We

Samantha Piper and Jun Matsui contributed equally to this review work.

J. Matsui · S. Piper · M. I. Boyer (✉)
Washington University in St. Louis, 660 S. Euclid Ave. Campus, Box
8233, St. Louis, MO 63110, USA
e-mail: miboyer@wudosis.wustl.edu

currently prefer a split thickness skin graft that is the thickness of a No. 15 scalpel blade using an electric dermatome, meshed for larger defects and unmeshed with pie-crusting for smaller wounds.

Several major recent advances in dressings applied to split thickness skin grafts—both to the graft and to the donor sites—have been described. An ideal dressing improves skin graft take, has minimal adhesion to the graft and skin irritation, and protects the healing wound. A soft silicone wound contact layer on the STSG site may reduce pain and time for dressing change compared with bridal veil and staples [1] with no significant difference in healing rates or total cost. A silk sericin-releasing bioactive dressing [2] for the treatment of proximal thigh STSG donor sites, when compared with a paraffin and chlorhexidine impregnated cotton dressing, was found to be less adherent to the wound, reached full healing 2 days earlier (12 days vs 14 days), and reduced pain in the first 4 postoperative days. Five different dressing materials on STSG donor site healing [3] were examined in an animal model. Fine mesh gauze, microporous polysaccharide hemosphere, clinoptilolite, alginate, hydrogel, and biosynthetic wound dressing (Biobran) were examined for healing rate and quality. Alginate produced the fastest and best quality healing, while hydrogel gave slower but good quality healing. The other dressings had poor quality healing. An oxygen-diffusing dressing for skin graft donor sites may decrease healing time and improve patient pain [4]. Other authors advocate an herbal extract gel [5] to reduce scarring and hyperpigmentation of the donor site.

Micrografting, a technique of using small donor sites to cover larger wounds by creating small islands of skin with increased surface area coverage, expands the coverage ability of the graft. The key tenet of micrografting is that the smaller the size of the skin piece, the larger its surface area relative to its volume. Submillimeter micrografts can be created by mincing a split thickness skin graft and accomplish wound healing and epithelialization in a 1:100 expansion ratio in an animal model, particularly when combined with moist dressings [6, 7]. While most hand wounds are small enough for coverage with conventional meshing techniques, micrografting offers an alternative in the setting of limited donor tissue, such as large burns.

Full thickness skin graft (FTSG)

Compared with split-thickness skin grafting, full thickness skin grafts have several advantages, including less contracture, improved contour, better durability, and better sensation due to reinnervation. However, they are associated with decreased adherence to the wound bed, and increased donor site morbidity, because they require split thickness skin graft coverage of the donor site if primary closure is not possible.

When large areas of coverage are needed, full thickness skin graft supply may be limited, particularly in the setting of burn injuries. Liposuction to deflate tissue and obtain primary closure of a full thickness skin graft site [8] allows for 1 stage harvest and closure of a large full thickness skin graft without the need for donor site coverage. Both STSG and FTSG are used to cover free flap donor sites. In 1 study comparing STSG and FTSG coverage of radial forearm free flap donor sites, there were no differences in time to healing at the donor or recipient sites, number of postoperative dressings, or postoperative pain [9], and a trend toward higher aesthetic scores in the FTSG group. Similarly, in a study of pediatric patients with palmar surface burns, pliability was significantly better in the FTSG group, though countered by increased hair growth [10]. There were no differences in sensation or number of contractures. Ultimately, the decision between STSG and FTSG should be made based on consideration of size of graft needed, and need for durability and minimal contracture. We prefer STSG from the proximal thigh for hand and forearm wounds when able, due to minimal donor site morbidity, and FTSG from the hypotenar hand for small finger and hand wounds due to lesser contracture and increased durability. In pediatric patients, we generally prefer STSG due to low donor site morbidity and good healing, but use FTSG for syndactyly releases.

Dermal substitutes

Recent literature has demonstrated that acellular dermal regeneration templates are effective for reconstruction of the dermis in full thickness upper extremity wounds after trauma and burns [11], or for coverage of flap donor sites [12]. The best-studied dermal substitute is Integra (Integra Life Sciences, Plainsboro, NJ), which consists of cross-linked bovine tendon collagen and chondroitin-6-sulfate formed into a porous bilaminate membrane. Integra has shown excellent outcomes in generation of a neodermis over deeper structures over 14–21 days, which can subsequently accept a skin graft.[13–16] Integra can be used in place of local flaps, resulting in less donor site morbidity, and has been shown to effectively cover exposed tendon, bone, joint, and exposed hardware in the absence of paratenon, periosteum, or joint capsule. Studies have shown a take rate of 76 %–98 %, which is improved if there is an adequate surrounding vascular bed [14–16]. Scar contracture and adhesion to underlying structures is decreased with Integra's inhibition of myofibroblast infiltration of the membrane, leading to improved tendon gliding and range of motion outcomes [16].

Traditionally, Integra has been used in a staged fashion, allowing for the dermal substitute to adhere and develop neovascularization for 1 to 7 weeks prior to skin grafting. This process can be accelerated by use of fibrin glue and negative

pressure wound therapy [11, 14]. A recent study by Demiri et al. suggests that application of both Integra and skin graft may be effectively performed as a single stage procedure [17]. They retrospectively reviewed outcomes of 8 patients who had simultaneous placement of single layer Integra and split thickness autograft skin for coverage of wounds ranging in size from 160–1250 cm [18]. After 1 week of compressive dressing, the patients began therapy, and at 12 months follow-up, had 95 % graft take, complete neovascularization of the Integra, and 83 % grip strength of the contralateral side.

In our practice, we do not use dermal substitutes; instead we prefer to perform autologous soft tissue transplantation whenever possible given its more consistent healing potential.

Local and distant flaps for thumb and thumb tip coverage

The thumb presents unique challenges for soft tissue coverage. In addition to being commonly used in grip and pinch, ideally, the volar pulp should be sensate for fine object discrimination, making skin grafting a poor option. Maintaining as much length as possible is more critical in the thumb in order to maintain pinch strength and dexterity, and revision amputation should be a last resort. Healing by secondary intention is reserved for wounds that are smaller than 1 cm x 1 cm, preferably partial thickness, without exposed bone.

The Moberg flap is a good option for volar thumb pulp injuries. It is a sensate axial pattern advancement flap. A full thickness skin and subcutaneous tissue volar flap is elevated, containing both radial and ulnar digital neurovascular bundles. The flap may be maximally advanced in a V-Y fashion after dividing all attachments except for the neurovascular bundles [19]. The interphalangeal (IP) joint may need to be flexed to allow closure of the flap over the exposed thumb tip. The excursion of the flap is limited, and requires extensive dissection and technical expertise. A common complication of the procedure is IP or MCP flexion contracture. A modification using the first web space skin as a transposition flap along with a Z-plasty to deepen the first web space to fill in the proximal defect from flap mobilization [20•] minimizes the need for thumb flexion and subsequent stiffness.

The cross finger flap from the dorsal index finger is another option for covering the volar thumb tip. A random pattern radially based skin and subcutaneous fat flap, this flap requires a full thickness skin graft over the extensor tendon epitenon in the donor site. When a dorsal branch of the proper digital nerve is brought with the flap, it can be made sensate. Index finger MCP flexion stiffness is a common complication.

Littler's heterodigital neurovascular flap from the radial (nondominant) aspect of the ring finger provides a sensate and pliable option for thumb tip coverage, but requires cortical reorientation in order to feel that the thumb is being touched rather than the ring finger. The ulnar side of the middle finger

has also been used as a potential donor site [21]. Several complications limit the wide use of this flap, including poor donor site circulation, cold intolerance, and poor sensibility of the donor site.

The first dorsal metacarpal artery flap (Kite flap) has been described for both volar and dorsal thumb wounds and may provide better overall hand function compared with the Littler flap [22] as well as good restoration of sensation on the thumb tip [23]. A second dorsal metacarpal artery flap has also been described [24] from the middle finger to cover a distal volar thumb injury. Like the kite flap, when used for dorsal thumb wounds, this flap would limit the need for excursion of the pedicle and potential compression as the pedicle was brought from dorsal to volar.

An antegrade pedicled flap taken from the proximal palm and distal forearm based on the superficial palmar branch of the radial artery to reconstruct a radial thumb wound was reported [25]. This flap provides glabrous skin coverage of the thumb. Further, a bone and nailbed composite graft from the amputated part of the thumb was recently described [26], with k-wire fixation to the stump, covered by a reverse homodigital dorsal ulnar flap with periosteum from the first metacarpal.

Finally, full thickness skin graft, though suboptimal due to being insensate, remains an option to maintain thumb tip length in those wounds that are not appropriate for shortening, as well as V-Y advancement, which would preserve sensation. We generally avoid pedicled transfers for smaller volar thumb tip injuries, using volar V-Y advancement or a cross finger flap from the index finger for coverage of these wounds (Table 1).

The dorsal aspect of the thumb, unlike the volar thumb tip, does not require sensation, and has mobile skin. Common local coverage options for the dorsal thumb include pedicled flaps based on the first dorsal metacarpal artery at the base of the index finger (kite flap) and random pattern dorsal skin rearrangements.

The Kite flap is based on the first dorsal metacarpal artery, and is elevated from the dorsal base of the index finger, tunneled under a skin flap, and can reach to the thumb IP joint. The donor site is covered with a split- or full-thickness skin graft. This provides an innervated, pliable, and versatile flap with minimal donor site morbidity [27]. Morbidity of the procedure includes diminished protective sensibility at the donor site, and thumb difficulty with precision grip, cold intolerance, and neuroma. Similar to Littler's flap for the volar thumb tip, the Kite flap requires cortical reorientation.

A cutaneous dorsoradial flap based on a cutaneous branch of the radial artery in the distal forearm provides a larger skin paddle but requires skin grafting of the donor site. [28] To provide a thin flap that minimizes donor site defects and provides a gliding surface for tendons, a pedicled reverse radial forearm adipofascial flap for a dorsal thumb defect may be used [29]. The donor site is closed primarily and the

Table 1 Volar thumb coverage options

	Description	Advantages	Disadvantages	Reference
Moberg	Axial pattern advancement flap	Sensate Does not affect other digits Volar thumb tissue used	IP or MCP joint stiffness	Harenburg 2012
Cross finger	Skin and subcutaneous fat random pattern flap	Local flap No tunneling Potentially sensate	Second procedure to divide the flap Index finger IP joint stiffness FTSG coverage of dorsal donor site	Vlastou 1985
Littler	Heterodigital neurovascular island flap	Versatile area of coverage Sensate	Lose sensation on donor site Cortical reorientation Tunneling risk of kinking Technically demanding Cold intolerance	Xarchas 2008
Kite	First dorsal metacarpal artery-based flap	Sensate Pliable	Technically demanding Distal extent limited Tunneling risk of kinking Cold intolerance Diminished protective sensibility of donor site Cortical reorientation	Foucher 1979
FTSG	Full thickness skin graft	Simple, technically straightforward Primary closure of donor site possible	Insensate Contracts	Hashem 2011

flap is covered with split thickness skin graft. A similar adipofascial flap, based on the proper digital artery elevated as a turndown flap from the proximal aspect of the thumb [30] is another option. Along these same lines, a reverse homodigital dorsal radial flap based on the dorsal radial artery of the thumb provides a good arc of rotation to reach distal dorsal thumb wounds [31]. We prefer using a Kite flap or groin flap for these wounds.

Local and distant flaps for finger and fingertip coverage

A variety of options have been described for treatment of soft tissue loss at the fingertip and finger, ranging from healing by secondary intention (if no bone is exposed) to complex flaps. At the fingertip, options include: the Atasoy (volar V-Y advancement flap for transverse or dorsal oblique tip amputations) [32], the Kutler (side V-Y advancement flap for midlateral tip amputations) [33], the first dorsal metacarpal artery island flap (for stump coverage) [27], and thenar and hypothenar flaps (for tip and pulp loss in young people) [33]. At the finger, options include: the side finger flap (for coverage of volar MCP defects), the lateral finger rotation or arterialized side finger flaps (for coverage of dorsal PIP defects) [33], cross-finger (for volar defects), and reverse cross-finger flaps (for dorsal defects) [34]. These are routinely used with success for finger and fingertip soft tissue coverage, however are often limited by local soft tissue

availability, donor site morbidity, need for a staged procedure, and recipient stiffness and scarring. In the last year, several groups have described novel techniques for soft tissue coverage that offer alternative options.

For fingertip injuries, recent literature has largely focused on restoration of sensation after amputation. Chen et al. described a rotational neurovascular cutaneous homodigital island flap that utilizes dorsal branches of the radial and ulnar digital nerves distally, which are cut and repaired to the volar branches after rotation around the dorsal branch of the digital artery, to restore tip sensation [35]. Several groups have also successfully used neurovascular homodigital island flaps based on the proper digital artery and nerve for restoration of sensation after finger pulp injuries in adults and children [36, 37]. The downside of these flaps is loss of donor site sensation. In all of these studies, there was excellent flap survival and restoration of fingertip sensibility and function. Hwang et al. have successfully reconstructed nail bed amputations with nail bed autografts from the amputated finger or first toe to restore a more normal appearing nail [38]. We prefer to allow for secondary wound healing in fingertip pulp injuries where no bone is exposed. For dorsal reverse oblique injuries with exposed bone, we use the Atasoy volar V-Y advancement flap, and we otherwise prefer the Kutler side V-Y advancement flap. This is used to cover the exposed bone, and the remainder of the wound is allowed to granulate in.

Several novel flaps have also been described for reconstruction of finger soft tissue loss. For volar finger defects

proximal to the distal interphalangeal joint, Chen et al. described a dorsal heterodigital neurocutaneous island flap designed to restore sensation and provide coverage [39]. This flap is taken from the dorsal aspect of an adjacent healthy finger, includes the dorsal branch of the digital nerve, and uses its related vascular network as the pedicle, thus, preserving the proper digital artery and nerve. This contrasts other heterodigital neurocutaneous flaps, such as the Littler flap, which harvest the proper digital artery and nerve. Advantages of this flap include preservation of donor finger sensibility, a single stage, and avoidance of microsurgical techniques. Chen et al. further modified this technique to allow the pedicle to reach past the distal interphalangeal joint by creating a bipediced heterodigital neurocutaneous flap that uses the dorsal branch of the digital nerve, the proper digital artery, and a dorsal vein [40]. For fingers with multiple soft tissue defects, Chen et al. have described the use of multiple dorsal homodigital island flaps using the dorsal branch of the digital artery and its associated vasculature at the pedicle [41]. For dorsal and dorsolateral finger defects, Namazi described a palmar island flap to use in place of a cross finger or reverse cross finger flap [42]. The flap is taken from palmar skin distal to the distal palmar crease, supplied by perforator from the superficial palmar arch and common digital arteries. Compared with a cross finger flap, which is commonly used to cover dorsal finger defects, this technique is a single stage, allows for primary closure of the donor site, and involves only the injured finger. Jian-min et al. described a pedicled split thickness skin graft from the abdominal wall to cover degloving injury of the finger [43]. Rather than take a bulky abdominal graft with subcutaneous tissue, this group took only the two-thirds of the dermis and sutured it to the degloved fingertip, allowing maintenance of length. All healed fully, suggesting an advantage to the dual blood supply from the pedicled graft. Disadvantages include a 2-stage procedure and motion restriction during the healing phase. In our practice, for dorsal wounds, we prefer a reverse cross finger flap, a homodigital adipofascial turnback flap, or a homodigital island flap. For volar wounds, we prefer a cross finger flap, a random pattern side finger flap, or a heterodigital island flap. We use arterialized side finger flaps, homodigital, or heterodigital island flaps, and reverse dorsal metacarpal artery island flaps for both dorsal and volar wounds. Our choice of flap varies depending on donor site availability and location of the wound.

Local and distant flaps for hand coverage

The volar and dorsal surfaces of the hand have distinct characteristics that lead to unique demands of their soft tissue coverage options. The palm, with its fine discriminatory

sensation and thick protective glabrous skin, requires similar coverage. The dorsal hand skin is much thinner and mobile, but requires minimal adhesion to underlying extensor tendons in order to maintain tendon gliding. The mobility of the dorsal skin often allows for skin rearrangement rather than requiring flap coverage.

Extensor tendons are unlikely to glide under muscle flaps. A STSG may be used in this region if there is sufficient epitenon covering the extensor tendons. A random pattern rectangular rotation flap may be taken from the dorsal hand and rotated to cover a dorsal defect. For larger or deeper defects, several island pattern local flaps are used to cover the hand, wrist, and forearm. These include the posterior interosseous artery flap, which preserves both major arteries to the hand, the reverse pedicle radial forearm flap, radial forearm fascial flap, radial forearm perforator flap, and ulnar artery flap. The posterior interosseous artery flap is an axial fasciocutaneous flap ideal for dorsal hand defects. The posterior interosseous artery flap provides coverage without sacrificing a major artery, but has a short pedicle with excursion limited to the dorsum of the hand [44]. A reverse thenar perforator flap is an option for volar hand coverage [45] that provides glabrous skin based on perforators from the superficial palmar branch of the radial artery, and can extend from the thenar crease to the proximal palmar crease. The donor site can be primarily closed, and the flap has wide applicability for palmar defects.

When the defect cannot be closed primarily, cannot support STSG or FTSG, and local tissue is not available or sufficient, distant axial pattern flaps are our option of choice. The groin flap is a versatile and reliable axial fasciocutaneous flap for dorsal or volar hand injuries, but disadvantages include the need for secondary operations, longer hospitalization, and arm immobilization [46]. Based on the superficial circumflex iliac artery located 2 cm distal to the inguinal ligament, the skin paddle can be designed to fit a large hand wound. We prefer groin flaps or free tissue transfer for larger hand wounds, and random pattern dorsal skin rearrangements for the dorsal hand when possible. If epitenon is present, a STSG is used. The posterior interosseous artery flap and reverse radial forearm flap are good options for medium sized hand wounds. For palmar wounds, we allow granulation or STSG of groin or abdominal flap coverage.

Use of negative pressure wound therapy in the hand

Negative pressure wound therapy (NPWT) has become a widespread tool for the treatment of both acute and chronic soft tissue defects. This successful technique facilitates granulation and healing through promotion of angiogenesis and cellular proliferation, wound contraction, edema reduction, and toxic exudate removal [47, 48]. It can be used alone to

expedite secondary wound healing, as a bridge between staged reconstruction procedures, or to promote healing after reconstructive procedures. A recent study described the use of NPWT in combination with oral tadalafil to increase vascularity and heal chronic finger ulcerations in a patient with scleroderma [49], emphasizing its potential for treatment of chronic wound in patients with vascular insufficiency. Granulation tissue and wound contraction induced by NPWT can shorten the time to soft tissue coverage and decrease the size of graft required [50, 51]. NPWT used as a bolster in conjunction with skin grafts and dermal substitutes leads to improved adhesion through prevention of sub-graft fluid collection and decrease of shear stress on the graft [52]. In the hand, complex 3-dimensional anatomy, the need for early mobility after injury, and the immediate subcutaneous location of nerves and tendons has limited the use of NPWT. Several techniques have been described to overcome these limitations.

One of these is the sterile glove technique, which has been described by several groups as a method for obtaining an adequate seal around the digits and web spaces and allowing for early mobility [49, 53, 54]. Kamolz et al. recently described 18 soft tissue defects in 12 patients requiring skin grafting after release of burn scar contracture were treated with the sterile glove technique of NPWT [55]. In this technique, a size matched sterile glove with the tips removed is used to cover the foam over the wound, and to provide a distal seal around fingers. The proximal band of the glove should be removed to prevent a pressure mark. Standard adhesive dressing is used to seal the proximal edge of the glove. The authors found 100 % skin graft take in this series, and the sterile glove technique was noted to be faster and easier to apply than standard adhesive dressings around the fingers and web spaces. There were no significant complications except 1 pressure sore from the proximal band of a glove, which was not removed. Sommer et al. emphasize that removal of the finger tips of the glove can allow for better monitoring of neurovascular status and early motion of the exposed digit [56].

Hagesawa et al. presented a case series using the application of a bag-type NPWT to the hand to allow for early mobility and therapy while continuing negative pressure wound care [57]. A hydrophilic sponge is applied to the wound and held in place with a porous adhesive film, then the entire hand is placed into a sterile sealing bag, taped at the forearm, which is subsequently attached to suction. The suction can be stopped to allow for early motion exercises several times a day, and then resumed at the end of each session. Four patients with varying wound location, size, and etiology had good healing results and on average gained 94.7 % total active motion of the contralateral hand after 3–8 weeks of bag-type NPWT.

A technique of functional splinting using gauze-based NPWT was recently described by Taylor et al. in the setting

of war related injuries [58]. This group found that unrolled Kerlix gauze placed directly against the skin, covered with adhesive film, and placed under –80 mmHg of suction could not only protect and stimulate wound healing in large soft tissue defects, but could also replace a plaster of Paris splint. Kerlix under suction was able to stabilize the hand in an intrinsic plus position, did not shrink as sterile foam often does, and did not cause skin maceration.

Aydin et al. have applied a custom negative pressure wound therapy dressing for secondary healing of fingertip injuries where primary closure is not possible and shortening is not desired [18]. A 20–50 milliliter syringe is attached to a 12–14-French feeding tube, which is connected to sterile medical foam covered by a sterile adhesive dressing over the fingertip. The syringe plunger is drawn and taped to another plunger to maintain the vacuum, then the syringe is taped to the forearm. Vacuum suction is reestablished twice daily or as needed. Further study is necessary to determine the specific advantage of this technique over standard wound care.

In our practice, we use negative pressure wound therapy primarily when staged debridement of a large wound is required. It is used as a dressing in between débridements until a stable, healthy wound bed is established, after which formal soft tissue coverage is performed. We generally do not use negative pressure wound therapy as a definitive treatment for soft tissue loss in the hand, except in the rare case where it can be used to form a layer of granulation tissue in a small dorsal wound, which is then covered with STSG.

Conclusions

Multiple options are available for soft tissue reconstruction of the hand, ranging from complex tissue transplantation to enhanced secondary wound healing. These provide the hand surgeon with a variety of tools to use to customize care for individual patients. Each option has advantages and disadvantages that influences choices for each patient's particular injury and functional needs.

Compliance with Ethics Guidelines

Conflict of Interest Jun Matsui's institution receives funding via a grant from AFSH 2010. Samantha Piper's institution receives funding via a OREF Resident Research Grant. Martin I. Boyer is a paid consultant for OrthoHelix and Acumed, LLC, has given paid expert testimony for Hand Surgical Medicolegal Consultation, LLC, and has stock/stock options with Tornier and OrthoHelix.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- Of major importance

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