Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jcot

Review Article

Management of diabetic foot: Brief synopsis for busy orthopedist

Tae Hwan Park^a, Ashish Anand^{b,*}^a Buleun Health Care Center, Incheon, Republic of Korea^b Staff Orthopaedic Surgeon, VAMC, Jackson, MS, USA

ARTICLE INFO

Article history:

Received 30 June 2014

Accepted 21 October 2014

Available online 14 November 2014

Keywords:

Diabetic

Wound

Flap

Reconstruction

ABSTRACT

According to available medical reports, over 10% of diabetic patients will develop foot ulcers during their lifetimes. This condition still remains great challenges to many clinicians. Various mechanisms may explain treatment-resistant entity. Treatment varies widely, relying on the severity of the ulceration as well as the presence of infection or ischemia. However, the most important things to keep in mind should consist of the following: 1) appropriate debridement; 2) off-loading of pressure; 3) effective control of infection; 4) local wound care strategy; 5) timely reconstructive surgery. The ideal flap for diabetic foot reconstruction should provide a well-vascularized tissue to control infection, adequate contour for footwear, durability, and solid anchorage to resist shearing forces. A thorough assessment of patient's general condition and voluntary motivation of the patient should be warranted to prevent any sort of postoperative recurrence.

Copyright © 2014, Delhi Orthopaedic Association. All rights reserved.

1. Introduction

According to available medical reports, over 10% of diabetic patients will develop foot ulcers during their lifetimes.¹ Diabetic foot ulcers are well known to many clinicians that they respond poorly to conventional treatment, making them very difficult to care.² Various mechanisms including neuropathy, arterial insufficiency, decreased expression of various growth factors, sustained inflammation, and increased apoptosis may explain these treatment-resistant entity.³ Over the last decade, significant advances have been made regarding the treatment of diabetic foot ulceration.⁴

Treatment varies widely, relying on the severity of the ulceration as well as the presence of infection or ischemia. However, the cornerstones of treatment for diabetic foot

ulcers regardless whether it is at past or in the present should consist of the following: 1) appropriate debridement; 2) off-loading of pressure; 3) effective control of infection; 4) local wound care strategy; 5) timely reconstructive surgery.

2. Diabetic foot management

2.1. Appropriate debridement

Debridement is necessary before application of other wound closure procedures and improves the overall outcome of the diabetic foot.⁵ Appropriate debridement causes activation of platelets (PLT) to control hemorrhagic responses and releases growth factors that initiate the cascade of wound healing process.⁶ After appropriate debridement, tissues should be kept

* Corresponding author.

E-mail addresses: ashishanandortho@yahoo.com, anandash@gmail.com (A. Anand).
<http://dx.doi.org/10.1016/j.jcot.2014.10.003>

0976-5662/Copyright © 2014, Delhi Orthopaedic Association. All rights reserved.

moist to prevent formation of devitalized tissue and subsequent deepening of the wound.⁷ However, excessive moisture is a risk factor for pressure sores, and other dermatitis.

2.2. Effective control of infection

Diabetic foot ulcers act as portals of entry for systemic infection⁸. Diabetic Foot infections have a wide range of spectrum from paronychia, cellulitis, myositis, abscesses, necrotizing fasciitis, septic arthritis, tendinitis, and osteomyelitis. Risk factors for OM can be summarized as follows: Appearance of a swollen, deformed red toe, visible or palpable bone on probing, infected ulcer with an ESR > 70 mm per hour, nonhealing ulcer after a few weeks of appropriate care and off-loading of pressure, radio logically evident bone destruction beneath ulcer, ulcer area >2 cm² or >3 mm deep, ulceration over bony prominences > two weeks, ulceration with unexplained leukocytosis. The most common pathogens in acute, previously untreated, superficial diabetic foot infection are aerobic G (+) bacteria (particularly staphylococcus aureus and beta-hemolytic streptococci), while MRSA is a more frequently encountered pathogen in diabetic patients who have recently received antibiotic therapy in a hospital.

Diabetic foot infections are one of the major causes of amputation. Hence effective control and prevention are very important to decrease morbidity and mortality of the patients.

Topical antimicrobial therapies such as liquid silver nitrate, silver sulfadiazine, and silver-coated dressings have been shown to eliminate bacteria in diabetic foot ulcers.⁹

2.3. Relief of pressure

Various new off-loading modalities are being investigated, because of the drawbacks of total contact casting. At low risk group, prevention, education and basic footwear advice will do. At moderate risk group, intensive footwear advice and special footwear for feet are recommend. If patients with recurrence diabetic ulceration, total contact cases, air casts, scotch cast boots, hope cast boot, heel shoe, wheel chair ambulation, or best rest are recommended. Two examples are removable cast walkers and half-shoes.^{10,11}

2.4. Local wound care strategy

2.4.1. Vacuum-drainage systems

Negative-pressure wound therapy has been shown to be beneficial in treating some soft tissue defects caused by diabetic foot wounds (Fig. 1).^{12–19}

This therapy should be considered in large foot ulcers and particularly post local amputation wounds. In addition, it is also indicated when satisfactory healing is not occurring after a 3-week implementation of the protocol.²⁰ Younan et al²¹ in their experimental study showed that vacuum-assisted closure therapy modulated nerve fiber and neuropeptide production in the wound. By optimizing the kinetics of vacuum-assisted closure application, clinicians can contribute to further improve wound healing in denervated wounds such as pressure sores and diabetic foot ulcerations.

Recently, Lerman et al introduced new ultraportable negative-pressure wound therapy devices reducing many

Fig. 1 – Showing wound vac in place.

disadvantages of previous products such as bulky and noisy characteristics, high cost and requiring an electrical power source.²²

2.4.2. Skin substitutes (e.g., Apligraf, Epifix)

Apligraf is a composite graft composed of a cultured living dermis and sequentially cultured epidermis and is derived from neonatal foreskin (Fig. 2).²³

Histologic comparison shows that Apligraf and human skin are very similar. Apligraf lacks Langerhans cells, melanocytes (epidermis level), any hair follicles, sweat glands, endothelial cells, or blood cells (dermis level). Instead of providing instant coverage, Apligraf instead serves as a vehicle for the delivery of growth factors and other cellular constituents essential to the normal wound healing process.^{23,24} Epifix is a dehydrated human amnion/chorion membrane allograft, which includes amnion and chorion. These 2 layers are a rich source of collagen, connective tissue, cytokines and growth factors. Hence Epifix provides a biological active matrix and growth factors for cellular ingrowth. Results have shown that Epifix contains one or more soluble

Fig. 2 – Showing dermagraft in place.

factors which can stimulate mesenchymal stem cell migration and recruitment.²⁵ There are no direct studies comparing the above modalities.

2.4.3. Blood bank platelet concentrate

According to Jeong et al,²⁶ the advantages of using a blood bank platelet concentrate as a source of growth factors in treating diabetic ulcers are as follows. First, many diabetic ulcer patients are hemodynamically unstable, and repeated blood sampling may harm patients. Second, the concentrated platelets can be obtained without the need for a platelet separation system. Third, this method obviates the time and effort required to locate a suitable donor for a homologous graft. Fourth, use of a blood bank platelet concentrate results in lower cost than other biotechnology products for non-healing diabetic foot ulcers.

2.4.4. Hyperbaric oxygen therapy

Several anecdotal and retrospective reports suggest that hyperbaric oxygen therapy may be of value for the treatment of diabetic foot wounds, and a few recent prospective studies have shown promising results.^{27–31}

Cochrane review concluded that hyperbaric oxygen therapy significantly reduced.

The risk of major amputation related to a diabetic foot ulcer.³²

However, the limited availability and complexity in process of treatment may distract our interest as a major adjuvant treatment option.

2.4.5. Pulsed electromagnetic fields

In 2008, Matthew et al conducted an experiment about the efficacy of novel “pulsed electromagnetic fields” using Db/db and C57BL6 mice. According to his experiment, pulsed electromagnetic fields accelerated wound closure in diabetic and normal mice. Pulsed electromagnetic fields can be considered as an option to accelerate wound healing under diabetic and normal conditions by up-regulation of FGF-2-mediated angiogenesis.

Pulsed electromagnetic fields also prevented tissue necrosis in response to a standardized ischemic insult.

2.4.6. Gene therapy using synthetic growth factors

Gene therapy is emerging as a powerful tool for treating diabetic foot.^{33–40} According to available literature, growth factors such as bFGF,⁴¹ PDGF-BB,^{40,42–45} EGF,^{36,46} rhBMP-2,⁴² HGF,³⁹ REGEN-D 150,³⁷ and EPO³⁸ can accelerate healing by stimulating granulation tissue formation and enhancing epithelialization.⁴⁵ This led to a statistically significant increase in angiogenesis and thicker, more collagen formation.⁴⁷ One of the other areas of focus is p53 which is a master cell cycle regulator and is up regulated in diabetics. It also plays regulatory roles in vasculogenic and apoptotic pathways.^{48–50}

In their^{48–50} experimental study on mice showed that by silencing the p 53 resulted in improved vasculogenesis and decreased apoptosis which improved healing of diabetic wounds.

Lee et al³⁵ in their study on mice showed that lentiviral PDGF transfection of the diabetic wound enhanced PDGF production, improved vascularization and collagen

organization, and has potential clinical applications in diabetic wound treatment.

However, due to the multitude of factors involved, the rapid degradation by wound proteases, and lack of a viable vehicle for sustained release, the development of a topically applied growth factor has been difficult.

Currently, the only commercially available product for diabetic foot ulcers is recombinant platelet derived growth factor-BB (becaplermin).^{42–44} Becaplermin is well tolerated and represents an innovative, pharmacologically active treatment for chronic lower extremity diabetic ulcers.⁵¹ This aqueous gel provides a moist wound healing environment with negligible systemic absorption.⁴³ Becaplermin gel is easy for patients or their caregivers to apply in a nonformal clinical setting, and published studies have shown that it has an excellent safety profile.^{40,51}

2.4.7. Stem cells therapy

The crux behind healing is to encourage blood supply. Following injury revascularization occurs and one third of this revascularization is harnessed by endothelial progenitor cells. Normally, ischemic insult induces the release of endothelial progenitor cells and other progenitor cells from the bone marrow.⁵² These cells are exported via blood circulation to the site of insult, where they participate in revascularization and tissue repair.⁵² In Diabetics not enough progenitor cells are seen at site of repair, the cause of which is a dysfunctional release mechanism in diabetes.⁵³ Also whatever progenitor cells are released into circulation have impaired migration/homing to peripheral sites of injury and decreased proliferation and differentiation once present in the wound.^{54–57} Warren et al⁵⁸ reported on their observations in mice when they showed that by using Single-dose topical application of lineage-negative progenitor cells to diabetic wounds was effective in significantly accelerating diabetic wound closure. By supplying the cells which were not recruited they by passed one of the mechanisms which was responsible for impaired healing. Recently, both bone marrow-derived stem cells, peripheral blood-derived endothelial progenitor cells, and human adipose-derived stem cells have been shown to accelerate healing in diabetic mice.^{59–61} According to Chan et al,⁶² a population of bone marrow-derived hematopoietic stem cells has the capacity to improve regeneration of diabetic wounds. Although understanding of exact mechanism of action of these cells is still under work, there have been increasing evidences that different stem cell populations play crucial roles in wound healing process. However, further future studies are warranted to investigate the mechanism of action of these hematopoietic stem cells.

2.5. Reconstructive surgery

Reconstructive therapies may be useful treatment options when the area of the diabetic foot ulcer has not decreased by more than 10% after the above mentioned.

Approaches have been applied for 2 months.⁶³

Despite the recent significant advances in microsurgery, its application to reconstruction of wounds in diabetic patients has been low.⁶⁴ The concerns regarding flap efficacy and viability, occlusion of flow to the distal limb, systemic

condition, patient compliance, and economical burden remain problematic.⁶⁵ When performing a microsurgical reconstruction of the diabetic foot, surgeons should follow some guidelines and preparation despite its controversies.

Angiogram is generally required to analyze the vascular patency of ATA (anterior tibial artery), PTA (posterior tibial artery), and PA (peroneal artery) for the reconstruction of diabetic foot.⁶⁶ A thorough assessment of patient's general condition and voluntary motivation of the patient should be warranted to prevent any sort of postoperative recurrence.

The ideal flap for diabetic foot reconstruction should provide a well-vascularized tissue to control infection, adequate contour for footwear, durability, and solid anchorage to resist shearing forces.

The use of fasciocutaneous flaps, muscle flaps with skin grafts, and diverse perforator flaps for reconstruction of the diabetic foot has been conducted successfully.^{64,65,67,68}

Considering its pros and cons, controversy still remains regarding which flap is the most reliable one. This endless question should be continued with the development of microvascular surgery techniques. In 2006, Hong et al favored the anterolateral thigh (ALT) perforator flaps for the management of the diabetic foot.⁶⁵ He also published a review article regarding the usefulness of a multidisciplinary approach along with an algorithm to manage and salvage diabetic foot ulcers from amputation and also found an interesting findings that diabetic foot reconstruction using free flaps increases overall 5-year-survival rate^{69,70}.

3. Conclusion

Numerous treatment methods including vacuum-drainage systems, skin substitutes especially Apligraf, blood bank

Fig. 3 – Treatment algorithm for diabetic foot ulcer.

platelet concentrate, hyperbaric oxygen therapy, pulsed electromagnetic fields, gene therapy using synthetic growth factors, and stem cells therapies have been proposed for local wound care of diabetic foot, suggesting that no single effective method has surfaced as the accepted standard. Proper selection among diverse local care modalities along with reconstructive microvascular treatment options including fasciocutaneous flaps, muscle flaps with skin grafts, and versatile perforator flaps would yield optimal wound management of diabetic foot. We propose the following algorithm (Fig. 3).

Conflicts of interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES

- Bennett MS. Lower extremity management in patients with diabetes. *J Am Pharm Assoc (Wash)*. Sep–Oct 2000;40(5 suppl. 1):S40–S41.
- Simms KW, Ennen K. Lower extremity ulcer management: best practice algorithm. *J Clin Nurs*. 2011 Jan;20:86–93.
- Mathes. *Plastic Surgery*. 2nd ed. vol. 1. Elsevier Health Sciences; 2005.
- Watkins PJ. The diabetic foot. *BMJ*. May 3 2003;326:977–979.
- Smith J. Debridement of diabetic foot ulcers. *Cochrane Database Syst Rev*. 2002;CD003556.
- Pelle MT, Miller 3rd OF. Debridement of necrotic eschar with 40% urea paste speeds healing of residual limbs and avoids further surgery. *Arch Dermatol*. Oct 2001;137:1288–1290.
- Wallace GF. Debridement of invasive diabetic foot infections. *Clin Plast Surg*. Oct 2007;34:731–734.
- Kampfer H, Schmidt R, Geisslinger G, Pfeilschifter J, Frank S. Wound inflammation in diabetic ob/ob mice: functional coupling of prostaglandin biosynthesis to cyclooxygenase-1 activity in diabetes-impaired wound healing. *Diabetes*. May 2005;54:1543–1551.
- Hanft JR, Fish SE, Frykberg R, Sage R, Sanders LJ. Wound management in the diabetic foot. *J Foot Ankle Surg*. May–Jun 1997;36:240–254.
- Armstrong DG, Short B, Espensen EH, Abu-Rumman PL, Nixon BP, Boulton AJ. Technique for fabrication of an “instant total-contact cast” for treatment of neuropathic diabetic foot ulcers. *J Am Podiatr Med Assoc*. Jul–Aug 2002;92(7):405–408.
- Kato H, Takada T, Kawamura T, Hotta N, Torii S. The reduction and redistribution of plantar pressures using foot orthoses in diabetic patients. *Diabetes Res Clin Pract*. Mar 1996;31:115–118.
- Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet*. Nov 12 2005;366:1704–1710.
- Chantelau E. Negative pressure therapy in diabetic foot wounds. *Lancet*. Mar 4 2006;367:726. author reply 726–727.
- Maegle M, Gregor S, Peinemann F, Sauerland S. Negative pressure therapy in diabetic foot wounds. *Lancet*. Mar 4 2006;367:725–726. author reply 726–727.
- Armstrong DG, Boulton AJ, Banwell P. Negative pressure wound therapy in treatment of diabetic foot wounds: a marriage of modalities. *Ostomy Wound Manage*. Apr 2004;50(4A suppl. 1):9–12.
- Sandison S. Negative pressure wound therapy promoted healing of diabetic foot ulcers more than advanced moist wound therapy. *Evid Based Nurs*. Oct 2008;11:116.
- Armstrong DG, Lavery LA, Boulton AJ. Negative pressure wound therapy via vacuum-assisted closure following partial foot amputation: what is the role of wound chronicity? *Int Wound J*. Mar 2007;4:79–86.
- Vikmatmaa P, Juutilainen V, Kuukasjarvi P, Malmivaara A. Negative pressure wound therapy: a systematic review on effectiveness and safety. *Eur J Vasc Endovasc Surg*. Oct 2008;36:438–448.
- Braakenburg A, Obdeijn MC, Feitz R, van Rooij IA, van Griethuysen AJ, Klinkenbijn JH. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. *Plast Reconstr Surg*. Aug 2006;118:390–397. discussion 398–400.
- Armstrong DG, Attinger CE, Boulton AJ, et al. Guidelines regarding negative wound therapy (NPWT) in the diabetic foot. *Ostomy Wound Manage*. Apr 2004;50(4B suppl. 1):3S–27S.
- Younan G, Ogawa R, Ramirez M, Helm D, Dastouri P, Orgill DP. *Plast Reconstr Surg*. 2010;126:87–96.
- Lerman B, Oldenbrook L, Eichstadt SL, Ryu J, Fong KD, Schubart PJ. Evaluation of chronic wound treatment with the SNaP wound care system versus modern dressing protocols. *Plast Reconstr Surg*. Oct 2010;126(4):1253–1261.
- Edmonds M. Apligraf in the treatment of neuropathic diabetic foot ulcers. *Int J Low Extrem Wounds*. Mar 2009;8:11–18.
- Streit M, Braathen LR. Apligraf—a living human skin equivalent for the treatment of chronic wounds. *Int J Artif Organs*. Dec 2000;23:831–833.
- Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. *Int Wound J*. 2013 Oct;10:493–500.
- Jeong SH, Han SK, Kim WK. Treatment of diabetic foot ulcers using a blood bank platelet concentrate. *Plast Reconstr Surg*. Mar 2010;125:944–952.
- Lebel D, Gortzak Y, Nyska M, Katz T, Atar D, Etzion Y. [Hyperbaric oxygen therapy for chronic diabetic wounds of the lower limbs—a review of the literature]. *Harefuah*. Mar 2007;146(3):223–227, 244–225.
- Hunter S, Langemo DK, Anderson J, Hanson D, Thompson P. Hyperbaric oxygen therapy for chronic wounds. *Adv Skin Wound Care*. 2010 Mar;23:116–119.
- Ong M. Hyperbaric oxygen therapy in the management of diabetic lower limb wounds. *Singapore Med J*. Feb 2008;49:105–109.
- Mutluoglu M, Uzun G, Yildiz S. Hyperbaric oxygen therapy in the treatment of diabetic foot ulcers—prudent or problematic: a case report. *Ostomy Wound Manage*. 2010 Jun;56:32–35.
- Niinikoski J. Hyperbaric oxygen therapy of diabetic foot ulcers, transcutaneous oxymetry in clinical decision making. *Wound Repair Regen*. Nov–Dec 2003;11:458–461.
- Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2004;CD004123.
- Man LX, Park JC, Terry MJ, et al. Lentiviral gene therapy with platelet-derived growth factor B sustains accelerated healing of diabetic wounds over time. *Ann Plast Surg*. Jul 2005;55:81–86. discussion 86.
- Badillo AT, Chung S, Zhang L, Zoltick P, Liechty KW. Lentiviral gene transfer of SDF-1alpha to wounds improves diabetic wound healing. *J Surg Res*. Nov 2007;143:35–42.
- Lee JA, Conejero JA, Mason JM, et al. Lentiviral transfection with the PDGF-B gene improves diabetic wound healing. *Plast Reconstr Surg*. Aug 2005;116:532–538.

36. Hong JP, Jung HD, Kim YW. Recombinant human epidermal growth factor (EGF) to enhance healing for diabetic foot ulcers. *Ann Plast Surg.* Apr 2006;56:394–398. discussion 399–400.
37. Mohan VK. Recombinant human epidermal growth factor (REGEN-D 150): effect on healing of diabetic foot ulcers. *Diabetes Res Clin Pract.* Dec 2007;78:405–411.
38. Galeano M, Altavilla D, Cucinotta D, et al. Recombinant human erythropoietin stimulates angiogenesis and wound healing in the genetically diabetic mouse. *Diabetes.* Sep 2004;53:2509–2517.
39. Yoshida S, Matsumoto K, Tomioka D, et al. Recombinant hepatocyte growth factor accelerates cutaneous wound healing in a diabetic mouse model. *Growth Factors.* Jun 2004;22:111–119.
40. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. *Plast Reconstr Surg.* Jun 2006;117(7 suppl. 1):143S–149S. discussion 150S–151S.
41. Uchi H, Igarashi A, Urabe K, et al. Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *Eur J Dermatol.* Sep–Oct 2009;19:461–468.
42. Al-Zube L, Breitbart EA, O'Connor JP, et al. Recombinant human platelet-derived growth factor BB (rhPDGF-BB) and beta-tricalcium phosphate/collagen matrix enhance fracture healing in a diabetic rat model. *J Orthop Res.* Aug 2009;27:1074–1081.
43. Cheng B, Liu HW, Fu XB, Sun TZ, Sheng ZY. Recombinant human platelet-derived growth factor enhanced dermal wound healing by a pathway involving ERK and c-fos in diabetic rats. *J Dermatol Sci.* Mar 2007;45:193–201.
44. Embil JM, Papp K, Sibbald G, et al. Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. *Wound Repair Regen.* May–Jun 2000;8:162–168.
45. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. *J Vasc Surg.* Jan 1995;21:71–78. discussion 79–81.
46. Hong JP, Park SW. The combined effect of recombinant human epidermal growth factor and erythropoietin on full-thickness wound healing in diabetic rat model. *Int Wound J.* 2014 Aug;11(4):373–378. <http://dx.doi.org/10.1111/j.1742-481X.2012.01100.x>. Epub 2012 Oct 19.
47. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. *J Am Coll Surg.* Jul 1996;183:61–64.
48. Jazayeri L, Callaghan MJ, Grogan RH, et al. Diabetes increases p53-mediated apoptosis following ischemia. *Plast Reconstr Surg.* 2008;121:1135–1143.
49. Ortega CC, Guzman GAM, Garcia RM. Hyperglycemia induces apoptosis and p53 mobilization to mitochondria in RINm5F cells. *Mol Cell Biochem.* 2006;281:163–171.
50. Nguyen PD, Tutela JP, Thanik VD, et al. *Suppl Plastic Reconstr Surg.* 2009;124:20–21.
51. Wieman TJ. Clinical efficacy of becaplermin (rhPDGF-BB) gel. Becaplermin Gel Studies Group. *Am J Surg.* Aug 1998;176(2A suppl. 1):74S–79S.
52. Kopp HG, Ramos CA, Rafi S. Contribution of endothelial progenitors and proangiogenic hematopoietic cells to vascularization of tumor and ischemic tissue. *Curr Opin Hematol.* 2006;13:175.
53. Tepper OM, Carr J, Chang C, et al. Diminished circulating progenitor cell number in diabetes is due to failed mechanisms of SDF-1-mediated mobilization. [Submitted for publication].
54. Tepper OM, Galiano RD, Capla JM, et al. Human endothelial progenitor cells from type II diabetic's exhibit impaired proliferation, adhesion, and incorporation into vascular structures. *Circulation.* 2002 Nov 26;106(22):2781–2786.
55. Abaci A, Oğuzhan A, Kahraman S, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation.* 1999;99:2239.
56. Chan RK, Liu PH, Pietramaggiore G, Ibrahim SI, Hechtman HB, Orgill DP. Effect of recombinant platelet-derived growth factor (Regranex) on wound closure in genetically diabetic mice. *J Burn Care Res.* 2006;27:202.
57. Coleman D. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia.* 1978;14:141.
58. Lin CD, Allori AC, Macklin J, et al. Wound healing in diabetic mice. *Plastic Reconstr Surg.* November 2008;122:1341–1351.
59. Sivan-Loukianova E, Awad OA, Stepanovic V, Bickenbach J, Schattman GC. CD34+ blood cells accelerate vascularization and healing of diabetic mouse skin wounds. *J Vasc Res.* Jul–Aug 2003;40:368–377.
60. Stepanovic V, Awad O, Jiao C, Dunnwald M, Schattman GC. Lepdb diabetic mouse bone marrow cells inhibit skin wound vascularization but promote wound healing. *Circ Res.* Jun 13 2003;92:1247–1253.
61. Kim EK, Li G, Lee TJ, Hong JP. The effect of human adipose-derived stem cells on healing of ischemic wounds in a diabetic nude mouse model. *Plastic Reconstr Surg.* Aug 2011;128:387–394.
62. Chan RK, Garfein E, Gigante PR, et al. Side population hematopoietic stem cells promote wound healing in diabetic mice. *Plast Reconstr Surg.* Aug 2007;120:407–411. discussion 412–403.
63. Steed DL, Attinger C, Brem H, et al. Guidelines for the prevention of diabetic ulcers. *Wound Repair Regen.* Mar–Apr 2008;16:169–174.
64. Karp NS, Kasabian AK, Siebert JW, Eidelman Y, Colen S. Microvascular free-flap salvage of the diabetic foot: a 5-year experience. *Plast Reconstr Surg.* Nov 1994;94:834–840.
65. Hong JP. Reconstruction of the diabetic foot using the anterolateral thigh perforator flap. *Plast Reconstr Surg.* Apr 15 2006;117:1599–1608.
66. Ciavarella A, Silletti A, Mustacchio A, et al. Angiographic evaluation of the anatomic pattern of arterial obstructions in diabetic patients with critical limb ischaemia. *Diabete Metab.* Nov–Dec 1993;19:586–589.
67. Rainer C, Schwabegger AH, Meirer R, Perkmann R, Ninkovic M. Microsurgical management of the diabetic foot. *J Reconstr Microsurg.* Nov 2003;19:543–553.
68. Hong JP, Shin HW, Kim JJ, Wei FC, Chung YK. The use of anterolateral thigh perforator flaps in chronic osteomyelitis of the lower extremity. *Plast Reconstr Surg.* Jan 2005;115:142–147.
69. Hong JP, Oh TS. An algorithm for limb salvage for diabetic foot ulcers. *Clin plastic Surg.* Jul 2012;39:341–352.
70. Oh TS, Lee HS, Hong JP. Diabetic foot reconstruction using free flaps increases 5-year-survival rate. *Journal of plastic, reconstructive & aesthetic surgery. JPRAS.* Feb 2013;66:243–250.