International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

To Compare the Efficacy of Betadine, Calcium Alginate and Recombinant Epidermal Growth Factor Dressing in Chronic Diabetic Ulcers

Viswanath Nallapaneni

Associate Professor, Department of General surgery, Katuri Medical College, Katurinagar, Chinakondrupadu, Guntur, India

Abstract: ***Diabetic ulcer is a common problem. No standard dressing is available. We have done this study to compare the efficacy of three types of dressings in chronic diabetic foot ulcers Diabetic with non-healing for more than 3 months with saline dressing was randomized into 3 groups of 30 each. A thorough clinical examination was done to exclude ischemia and Xray to exclude osteomyelitis. Location of ulcer was noted. The wound size was measured by cutting a gauge piece to the size of the wound and placed over the graph paper. Group I received Betadine soaked gauge, II Calcium Alginate Fibers (Sorbalgon) and III Recombinant Epidermal Growth Factor gel (Eugraf 150 mcg gel) dressing minimum twice weekly, besides treatment of diabetes and co morbidities for 12 weeks. At the end of twelve weeks ulcers were assessed for healing. Calcium alginate is the significantly effective dressing in comparison to betadine and Eugraf. No significant difference in healing with Eugraf in comparison to betadine.***

Keywords: Chronic diabetic ulcer, Dressing, Betadine, Calcium alginate, and Epidermal growth Factor

1. Introduction

The prevalence of diabetes mellitus is growing at epidemic proportions in the India and worldwide[4]India is known as Diabetic capital of the world[5]. Foot disorders are a major source of morbidity and a leading cause of hospitalization for persons with diabetes. Ulceration, infection, gangrene, and amputation are significant complications of the disease, estimated to cost billions of dollars each year. Charcot foot due to diabetic neuropathy is another serious complication, in addition to diabetic foot ulcers, which is the leading precursor to lower extremity amputation in diabetic patients[6] Clinicians must determine how to more effectively prevent ulceration. Although not all diabetic foot disorders can be prevented, it is possible to effect dramatic reductions in their incidence and morbidity through appropriate evidence-based prevention and management protocols

2. Aim, Objective & Methods

To compare the efficacy of Betadine, Calcium Alginate (Sorbalgon) and Recombinant Epidermal Growth Factor (Eugraf) dressing to treatment of chronic diabetic ulcers due to neuropathy, infection or both. Thirty patients were included in the study for each of the three dressings.

Inclusion criteria

1. Diabetic with ulcer not healing for three months.

Exclusion criteria

1) Patient presenting to hospital with frank gangrene of toes or foot.
2) Patients with vascular impairment leading to ulceration.
3) Doppler showing blocked or diminished flow in > 2 vessels.
4) Patients with radiologically proven osteomyelitis.

Diabetic with ulcer more than 3-month duration coming to our hospital were included in the study. After a through clinical examination, they were investigated. Besides the routine hematological, biochemical parameters for renal, liver function, USG Doppler for vascular evaluation and x-ray of the part were done to look for any evidence of osteomyelitis. Control of sugar was checked by blood sugar and glycoselated haemoglobin estimation periodically. The cases with gangrene of toes or foot indicating severe ischemia and osteomyelitis on plain X-ray were excluded from the study. Wound swab was taken for culture in all cases and antibiotics were given where necessary as per the sensitivity pattern. Good glycemic control was ensured by diabetic diet and adjusting the dosages of anti diabetic therapy used before by the patient, either insulin or oral hypoglycemic agent. Any cases having dead and devitalized tissue were taken up for wound debridement. And after the initial through debridement the dressings were started and subsequent debridement were done as and when requirement basis. The cases were randomized into 3 groups by sealed envelope method for different types of dressing Group I was given 5% Povidon iodine (Betadine from Lupin India) Group II – Calcium Alginate fiber (Sorbalgon 10 x 10 cm from Hartmann, Germany) and Group III – Recombinant Epidermal Growth Factor (rEGF) (Eugraf from Lupin India, 150mcg in 15 gm tube gel). At this stage the wound size was measured by cutting a gauge piece to the size of the wound and same was placed over the graph paper, which gives almost sq mm accuracy of total surface area of ulcer. In all the dressing the wound was cleaned initially with normal saline and the specific agent dressing were applied without any anaesthesia in the minor OT/ ward dressing room. Initially the dressing was done under the supervision by the guide and later after standardization by the author twice weekly on indoor/OPD basis. All the cases and their relatives were informed about the day and date of the next dressing and were told to come back as soon as the dressing become soaked till outer layer. In Group I (Betadine dressing) a betadine soaked gauge piece, in the II group Alginate fiber was in placed covering the wound and a dry gauge piece was applied over the wound. In the third group the rEGF gel was applied and saline moist gauge piece was

placed over the gel. All the three groups were then given loose bandage so as dressing medicament remain in place inside the covered wound. All the cases were advised to use covered foot-ware so as to avoid trauma and to keep the dressing in situ. Each case the same type of dressing was given for 12 weeks. All the wounds were measured twice weekly during the dressing time and final measurement done at the end of twelve weeks with the variation of max two days after exposing and cleaning wound as done initially. The difference between the initial and final measurement was taken into account for analysis of results. The cost of twelve-week treatment was evaluated by including the cost of medicine, the sterile gauge piece and bandage. Manpower cost was not included.

Statistical Analysis – The end for the treatment was complete healing of the ulcer after twelve weeks of therapy. Sample size of 30 each was considered adequate. The non-healing group was divided as more than 50% healing and less than 50% healing. The less than 50% were considered non-healing while doing the calculation. The calculation done based upon null hypothesis. The endpoints of the comparable two groups at a time were done by ChiSquare test and by calculation of odd ratio with 95 % confidence interval. P value < .05 was considered significant

3. Results

Patients - Total 96 patients were recruited for the study. In one patient X-ray of foot was suggestive of osteomyelitis of first metatarsal and two had Doppler confirmed ischemia. These patients were excluded from the study. Two patients have to undergo amputation as they developed uncontrolled sepsis in Cal Alginate group. One patient lost follows up in Eugraf dressing group. Finally ninety patients were analyzed.

Age distribution - Youngest patient was 40 years old and eldest was 92 years old. Mean age was 62.22 years (SD 9.18 yrs).

Type of Diabetes mellitus - All were Type II Diabetes Mellitus.

Duration of diabetes – Duration varied from three years to thirty years. Mean duration of diabetes was 9.5 years (SD 5.07).

Sex distribution - Total Male patients were 57 and female patients were 33. M: F: 63:37(1.7:1).Incidence is more common in males as they are exposed to external environment more as compared to females. Trauma is also more common in males leading to diabetic foot ulcer. The main text for your paragraphs should be 10pt font. All body paragraphs (except the beginning of a section/sub-section) should have the first line indented about 3.6 mm (0.14").

Addictions - Twenty-four patients out of ninety (26.6%) were active smokers/alcohol consumers during the presentation with ulcer. All the females were non-smoker.

Considering the males alone 42.1% were smokers. Any body that had stopped this habit six-month prior was not included.

Socioeconomic status -Nine (10%) patients belong to good socioeconomic strata(monthly income >20,000).

Location of ulcer - Most of the patients had ulcer on the foot (77/90 – 85%). Others had ankle, leg or sacral ulcer. Diabetic Ulcers are commonest on extremity as extremities are exposed to trauma. Shoe injuries also contribute to diabetic foot ulcer. Other contributing factors age microangiopathy, neuropathy, or combination of both. Studies have also proven these to be the etiological factors.

Ulcer size - Minimum ulcer size was 1 cm^2 and maximum was 35 cm^2 .Mean ulcer size was 5.86 cm2 (SD 5.62).

History of previous ulcer and amputation - Sixty-one patients out of ninety (67.7%) had history of previous healed ulceration and most of them had foot ulcer. Twenty-three (25.5%) patients had undergone amputation previously due to diabetic foot ulcer complication and all these patients had history of ulceration. Two of the alginate group requiring amputation during study was previous amputees.

Previous dressings - All patients were undergoing saline dressing prior to be included in study.

Duration of ulcer - Minimum duration of ulcer was three months and maximum was eight months. Mean ulcer duration was 4.2 months (SD 1.31).

Etiology of ulcer - Forty-two (46.6%) patients had ulcer of infective etiology started in inter-digital space and then spread proximally. Thirty-eight (42.2%) patients had ulcer of traumatic origin which patient did not noticed initially and get infected secondarily. Most of traumatic ulcers started at tip of the toe as patients were wearing proper footwear. Ten (11.1%) patients had pressure ulcers on the heel and on plantar aspect at the level of head of first metatarsal. These patients were either bed ridden or not using the proper footwear.

Systemic disease - 80 (88.9%) patients had associated systemic disease like Hypertension, Coronary Artery Disease or Chronic Kidney Disease. 21 (23.3%) patients had hypertension alone.40 (44.4%) patients had hypertension with CAD. 19 (21.1%) patients had HTN, CAD and CKD.

X- Ray - X-ray was done in all patients. In two patients X-ray was suggestive of osteomyelitis and were excluded from the study. In rest of patients there was no bone involvement but osteoporosis was noticed in significant number of cases.

Doppler - In two patients clinical examination suggestive of critical limb ischemia, which was confirmed on Doppler. These patients were excluded from the study.

Wound Swab Cultures - In 58 patients (64.4%) wound swab culture was sterile. In 30(33.3%) cases wound swab culture grown Staphylococcus. In one patient each (2.2%) swab has grown Proteus and Citrobactor. Antibiotics were given only to the patients where culture was positive as per sensitivity.

Healing with dressing
5 (17%) patients on betadine dressing shows complete wound healing. 24 (80%) patients on Cal Alginate dressing shows complete wound healing. 11 (36.6%) patients on Eugrf dressing shows complete wound healing. Calcium alginate is the significantly effective dressing in comparison to betadine and Eugraf (P<. 001)(table No 2). No significant difference in healing with Eugraf in comparison to betadine (P>.05) (table No 2).

Dressing	No of Patients	Complete healing	Reduction in size> 50%	No healing
Betadine	30	5(17%)	7(23%)	18(60%)
Calcium Alginate	30	24(80%)	6(20%)	0
Eugraf	30	11(36.6%)	12(40%)	7(23.3%)

	Betadine	Eugraf	Cal Alginate	P Value
Non healing	25	19	6	
Complete healing	5	11		**> .05**
Complete healing	5		24	**< .001**
Complete healing		11	24	**< .001**

Time for complete healing –Betadine Dressing - Average healing time for complete healing for completely healed ulcers was 11.5 weeks (SD 1.00)

Eugraf Dressing - Average healing time for complete healing for completely healed ulcers was 10 weeks (SD 1.88)

Cal Alginate - Average healing time for complete healing for completely healed ulcers was 9.1 weeks (SD 2.42)

Cost of Dressing –
Average cost of Betadine dressing per patient over twelve weeks was Rs 787 (SD 57)
Average cost of Eugraf dressing per patient over twelve weeks was Rs 4886 (SD 1062)
Average cost of Cal Alginate dressing per patient over twelve weeks was Rs 1186 (SD226).

Follow up – Pts were followed up after 12 weeks of treatment with specific dressing type of dressing. In the patients where there was either sub optimal response or no response to the specific dressing had undergone skin grafting of Cal Alginate dressing. Patients later changed to Cal Alginate dressing where not included in study.

4. Discussion

Patients – India is the diabetic capital of the world[5]We have significant number of the patients with diabetic foot ulcer reported to our hospital in last two years. Study included only patients with neuropathy, infection and both.

Age and Sex Distribution – Diabetes is the disease of old age. Mean age in our study was 62.5 years, which correlates with the other studies where they have reported the mean age around 65 years[9, 10]. Diabetic foot complications increase with the duration of diabetes. The study shows recurrent ulceration and multiple amputations common with long standing diabetes17-20. Present study also had similar finding. In our study diabetic foot ulcers were seen more commonly in males as compared to females. Increase Incidence in males may be because they are exposed to external environment more as compared to females, which is prevalent in Indian society. Trauma is also more common in males leading to diabetic foot ulcer. Repeated foot trauma due to ill-fitting shows my also be the contributing factor which was seen in other studies[57, 64, 69, 74, 75].

History of previous ulcer and amputation – History of healed ulceration andamputation are important risk factor for diabetic foot ulceration[37, 38]. In our study 67% patients had history of previous healed foot ulcers and 25% had amputation. This may be due to increase life expectancy with diabetes82, 89. Risk of amputation in patients with diabetic ulcer in our study group was 2.3 %. Other studies has shown amputation rate varying from 2% to 16 %110,111

Duration of ulcer – Long duration ulcers can lead to extensive tissue necrosis and gangrene, requiring amputation to prevent more proximal limb loss. This includes soft tissue infection with severe tissue destruction, deep space abscess, or osteomyelitis[114].The mean Duration of ulcer in the present study was 4.2 months. We had excluded the osteomyelitis cases. In spite of this we had 2 amputations (2.3%) during study period.

Etiology of ulcer - Risk factors include peripheral neuropathy, micro and macro angiopathy, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and impaired visual acuity [37,38]. This study had almost same risk factors except the macroangiopathy, which was excluded from the study by using Doppler. 46.6% patients had ulcer of infective etiology started in inter-digital space and then spread proximally. Nonhealing wounds can become stuck in the inflammatory phase of healing, increasing cytokine response with subsequent elevatedprotease levels and impaired growth factor activity[148, 149, 150].Present study has not done any evaluation of growth factors. 42.2% patients had ulcer of traumatic origin which patient did not noticed initially and get infected secondarily. Most of traumatic ulcers started at tip of the toe as patients were wearing improper footwear. Ten (11.1%) patients had pressure ulcers on the heel and on plantar aspect at the level of head of first metatarsal. These patients were either bed ridden or not using the proper footwear. Combination of Similar factors leading to ulcer formation are reported[37,38].

Systemic disease - Cardiovascular complications are the most common cause of premature death among patients with diabetes[12]. Other common co morbidities are hyperglycemia and vascular diseases such as cerebral vascular accidents, transient ischemic attacks, myocardial infarctions, angina, valvular heart disease, atrial fibrillation, aneurysms, renal dysfunction, hypertension, hypercholesterolemia, and hyperlipidemia[143]. In present study 88.9% patients had associated systemic disease like Hypertension; Coronary Artery Disease (CAD) or Chronic Kidney Disease (CKD). 23.3% patients had hypertension alone. 44.4% patients had hypertension with CAD. 21.1% patients had HTN, CAD and CKD. Because diabetes is a multi-organ systemic disease, all co morbidities that affect wound healing must be assessed and managed by a multidisciplinary team for optimal

outcomes in the diabetic foot ulcer[142]. That is why we had treated all our cases with co morbidities in consultation with vascular surgeon, cardiologist and nephrologists.

Imaging - Imaging play an important role in the assessment and evaluation of the diabetic foot ulcer. Plain x-rays are indicated based on the extent, nature of the ulcer, and clinical change in the appearance of the ulcer or failure to heal29. In our study we had done imaging in form of x-ray, Doppler. In two patients X-ray was suggestive of osteomyelitis. Persons with diabetes have an increased risk for developing an infection of any kind and a several-fold risk for developing osteomyelitis[103]. Most of our cases that were having sepsis were due to uncontrolled hyperglycemia. Two had osteomyelitis and two patients without osteomyelitis-required amputation because of fulminant sepsis.

Peripheral Arterial Disease (PAD) rarely leads to foot ulcerations directly. However, once ulceration develops, arterial insufficiency will result in prolonged healing, imparting an elevated risk of amputation [76, 77].In two patients with suspicion of ischemia, Doppler was confirmatory. Attempts to resolve any infection will be impaired due to lack of oxygenation and difficulty in delivering antibiotics to the infection site. Therefore, early recognition and aggressive treatment of lower extremity ischemia are vital to lower limb salvage [78, 79, 80].

Wound Swab Cultures - The diabetic foot infections are frequently polymicrobial [105]. In this study majority 64.4% reported as sterile possibly we recruited previously treated cases even with antibiotics and in 33.3% wound swab culture grown Staphylococcus. In one patient each (2.2%) swab has grown Proteus and Citrobactor. Surprisingly we could not isolate mixed organism from our culture study. We cannot explain this variation. Possibly we have taken the culture in the phase of callus ulcer. We have taken very few tissue specimen cultures, which might have given mixed bacteriology. Tissue specimens collected by curettage or biopsy are preferred, because they provide more accurate results than superficial swabs[151].

Healing – In our study healing with Cal Alginate dressing was significantly better ($p < .001$) than betadine and Eugraf Dressing. Statistically there was no significant difference in healing with Eugraf Dressing as compared to betadine dressing. Studies has proved faster and better wound healing with calcium alginate as compared to saline dressing[238].Recently one report found hypercalcemia with use of large quantity of calcium alginate dressing on a large surface area burnt wound[239]. We have not had similar experience, possibly because of small ulcer size. Calcium alginates can create the ideal environment for wound healing and reduce healing times. Alginate dressings facilitate an optimum environment for healing and are useful in the management of exudate[240]. The literature suggests that alginates are not painful at dressing change. We have noticed same, less painful dressing change in our alginate group. Alginate can reduce healing times compared with other types of dressing like collagen and saline[241]. When used appropriately, alginates facilitate trauma-free dressing removal and are conformable and easy to use, with high levels of absorbency. The gelling action of alginate dressings creates warm moist environment that is ideal for wound healing. Pressure ulcers treated with alginate dressings showed favorable results when compared with those treated with dextranomer paste dressings[242]. Alginates have been shown to be of benefit in moderate to highly exuding wounds because of following reasons -

1) The haemostatic properties of alginate dressings high in calcium may be useful for podiatrists in arresting small bleeding points during the sharp debridement of neuropathic ulcers242.
2) Alginate dressings high in mannuronic acid, which consequently form only a weak gel on contact with exudate, may have a place in managing wounds with a sinus as they are less likely to plug and can be flushed easily with saline[242].
3) Alginate dressings are conformable and flexible, and because they come in small sizes, they are easily used on areas of the foot that are difficult to dress[242].

Even betadine is the long standing dressing chemical no literature available on rate of wound healing. We have found no benefit of betadine dressing. The non-healing and partial healing was maximum. This corroborates with lack of literature on this context as negative findings are neither reported nor get published.

Recombinant human epidermal growth factor (EGF) stimulates the proliferation and migration of epithelial cells in human culture systems[231]. EGF has been shown to enhance wound healing. Besides growth factor, other extracellular signals, including disruption of cell –cell or cell matrix contact and the provisional matrix might contribute to the initiation of migration re-epithelization, and activation of gene expression230. There is no study available, which has compared EGEF with other dressing. Our results show it is significantly inferior to alginate ($p < .001$). However, we have got better healing rate with EGF dressing than betadine, which is not statistically significant ($p > .05$). The cost of 12 weeks dressing per patient with Betadine, Alginate and Eugraf has come to Rs 787, Rs 1186 and Rs 4886 respectively. Most likely the cost of EGF is prohibitive for routine dressing.

It is clear that dressings are only one element in the holistic management of this patient group. Diabetic foot ulceration is a recognized complication of diabetes and can never be managed in isolation. In addition to dressing selection, emphasis must be placed on good glycaemic control, pressure reduction, appropriate antibiotic therapy and skilled debridement.

5. Conclusion

1) Foot ulcer is seen minimum 3 years after initiation diabetes.
2) Calcium alginate is the significantly effective dressing in comparison to betadine andEugraf ($p < .001$).
3) No significant difference in healing with Eugraf in comparison to betadine ($p > .05$).
4) Eugraf is costliest and betadine is least costly but both are less effective in ulcer healing.
5) Dressing change least painful and less frequent with

Alginate.

References

[1] Broughton G 2nd, Jans JE, Attinger CE. A brief history of wound care. Plast Reconstr Surg 2006; 117:6S-11S.
[2] Sipos P, Gyory H, Hagymasi K, et al. Special wound healing methods used in ancient Egypt and the mythological background. World Journal of Surgery 2004;28:211-16
[3] Lee J. Sanders. From Thebes to Toronto and the 21st Century: An Incredible Journey. Diabetes Spectrum January 2002 15:56-60.
[4] Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005; 366:1719-1724.
[5] Shashank R Joshi, Rakesh M Parikh. JAPI Vol 55:2007; 323-324.
[6] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005; 293:217-228.
[7] International Diabetes Federation and International Working Group on the Diabetic Foot. Diabetes and Foot Care: Time to Act, International Diabetes Federation, Brussels, 2005.
[8] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27:1047-1053.
[9] American Diabetes Association. Diabetes 1996 Vital Statistics, American Diabetes Association, Alexandria, VA, 1996.
[10] Harris MI. Diabetes in America: Epidemiology and scope of the problem. Diabetes Care. 1998; 3: S11-S14.
[11] American Diabetes Association. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2000; S4-S19.
[12] American Diabetes Association. Diabetes Facts and Figures, 2000, American Diabetes Association, Alexandria, VA, 2000; 1 – 12.
[13] Palumbo PJ, Melton LJ. Peripheral vascular disease and diabetes. In: Harris MI, Hamman RF editor. Diabetes In America. Bethesda: National Institutes of Health; 1985;p.1 21.
[14] Reiber GE. Epidemiology of foot ulcers and amputations in the diabetic foot. In: Bowker JH, Pfeifer MA editor. The Diabetic Foot. St. Louis: Mosby; 2001;p.13-32.
[15] Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: Harris MI, Cowie C, Stern MP editor. Diabetes in America. 2nd ed. NIH Publication No. 95; 1995;p.409-427.
[16] Frykberg RG, Habershaw GM, Chrzan JS. Epidemiology of the diabetic foot: ulcerations and amputations. In: Veves A editors. Contemporary Endocrinology: Clinical Management of Diabetic Neuropathy. Totowa, NJ: Humana Press;1998;p.273, last page.
[17] Moss SE, Klein R, Klein BEK. The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med. 1992; 152:610-616.
[18] Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care. 1999; 22:382-387.
[19] Kumar S, Ashe HA, Parnell LN, Fernando DJ, Tsigos C, Young RJ, et al. The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. Diabetic Med. 1994; 11:480-484.
[20] Moss SE, Klein R, Klein BE. The 14-year incidence of lower extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care. 1999; 22:951-959.
[21] Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care. 1998; 21:1071-1075.
[22] Walters DP, Gatling W, Mullee MA, Hill RD. The distribution and severity of diabetic foot disease: a community study with comparison to a non-diabetic group. Diabet Med. 1992; 9:354-358.
[23] Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower extremity ulcers in patients with diabetes from two settings. Diabetes Care. 1999; 22:157-162.
[24] Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Physician. 2002; 66:1655-1662.
[25] Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A. Role of neuropathy and high foot pressures in diabetic foot ulceration. Diabetes Care. 1998; 21:1714-1719.
[26] Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care. 1999; 22:1036-1042.
[27] Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care. 1990; 13:513-521.
[28] Larsson J, Agardh CD, Apelqvist J, Stenstrom A. Long-term prognosis after healed amputation in patients with diabetes. Clin Orthop. 1998; 350: 149-158.
[29] American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care. Diabetes Care. 1999; 22:1354, last page.
[30] Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. Wound Repair Regen. 2005; 13:230-236.
[31] Tentolouris N, Al-Sabbagh S, Walker MG, Boulton AJ, Jude EB. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. Diabetes Care. 2004; 27:1598-1604
[32] Mayfield JA, Reiber GE, Maynard C, Czerniecki JM, Caps MT, Sangeorzan BJ. Survival following lower-limb amputation in a veteran population. J Rehabil Res Dev. 2001; 38:341-345
[33] Frykberg RG. Epidemiology of the diabetic foot: ulcerations and amputations. Adv Wound Care. 1999; 12:139-141.

[34] Gibbons GW, Eliopoulos GM. Infection of the diabetic foot. In: Kozak GP, Campbell DR, and Frykberg RG, Habershaw, GM editor. Management of Diabetic Foot Problems. Philadelphia: WB Saunders; 1995;p. 121, last page.
[35] Shaw JE, Boulton AJ. The pathogenesis of diabetic foot problems: an overview. Diabetes. 1997; 46:S58-S61.
[36] Boulton AJ, Meneses P, Ennis WJ. Diabetic foot ulcers: a framework for prevention and care. Wound Repair Regen. 1999; 7:7-16.
[37] Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med. 2004; 351:48-55.
[38] Boulton AJ. The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia. 2004; 45:1011–1016.
[39] Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, et al. The Northwest Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community based patient cohort. Diabet Med. 2002; 19:377-38.
[40] Edmonds ME, Blundell MP, Morris ME, Thomas EM, Cotton LT, Watkins PJ. Improved survival of the diabetic foot: the role of a specialized foot clinic. Q J Med. 1986; 60:763-771.
[41] Akbari CM, Macsata R, Smith BM, Sidawy AN. Overview of the diabetic foot. Semin Vasc Surg. 2003; 16:3-11.
[42] Bus SA, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. Diabetes Care. 2002; 25:1444-1450.
[43] Sumpio BE. Foot ulcers. N Engl J Med. 2000; 343:787-793.
[44] Van Gils CC, Roeder B. The effect of ankle equinus upon the diabetic foot. Clin Podiatr Med Surg. 2002; 19:391-409.
[45] Lin SS, Lee TH, Wapner KL. Plantar forefoot ulceration with equinus deformity of the ankle in diabetic patients: the effect of tendo-achilles lengthening and total contact casting. Orthopaedics. 1996; 19:465-475.
[46] Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med. 1998; 158:158-162.
[47] Armstrong DG, Stacpoole-Shea S, Nguyen H, Harkless LB. Lengthening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. J Bone Joint Surg Am. 1999; 81:535-538.
[48] Van Schie CH. A review of the biomechanics of the diabetic foot. Int J Low Extrem Wounds. 2005; 4:160-170.
[49] Lavery LA, Armstrong DG, Boulton AJ. Ankle equinus deformity and its relationship to high plantar pressure in a large population with diabetes mellitus. J Am Podiatr Med Assoc. 2002; 92:479-482.
[50] Mueller MJ, Sinacore DR, Hastings MK, Strube MJ, Johnson JE. Effect of achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. J Bone Joint Surg. 2003; 85A: 1436-1445.
[51] Flynn MD, Tooke JE. Aetiology of diabetic foot ulceration: a role for the microcirculation. Diabetic Med. 1992; 8:320-329.
[52] Parkhouse N, Le Quesne PM. Impaired neurogenic vascular response in patients with diabetes and neuropathic foot lesions. N Engl J Med. 1988; 318:1306-1309.
[53] Boulton AJM, Vileikyte L. Pathogenesis of diabetic foot ulceration and measurements of neuropathy. Wounds. 2000; 12:12-18
[54] Boulton AJ. The pathogenesis of diabetic foot problems: an overview. Diabet Med. 1996; 13: S12-S16.
[55] Nabuurs-Franssen MH , Houben AJ , Tooke JE , Schaper NC. The effect of polyneuropathy on foot microcirculation in Type II diabetes. Diabetologia. 2002; 45:1164 - 1171.
[56] Frykberg RG. Biomechanical considerations of the diabetic foot. Lower Extremity. 1995; 2:207-214.
[57] Knox RC, Dutch W, Blume P, Sumpio BE. Diabetic Foot Disease. Int J Angiology. 2000; 9:1-6.
[58] Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. Diabetologia. 1992; 35:660-663.
[59] Robertson DD, Mueller MJ, Smith KE, Commean PK, Pilgram T, Johnson JE. Structural changes in the forefoot of individuals with diabetes and a prior plantar ulcer. J Bone Joint Surg Am. 2002; 84: 1395-1404
[60] Greenman RL, Khaodhiar L, Lima C, Dinh T, Giurini JM, Veves A. Foot small muscle atrophy is present before the detection of clinical neuropathy. Diabetes Care. 2005; 28:1425-1430.
[61] Mueller MJ, Hastings M, Commean PK, Smith KE, Pilgram TK, Robertson D, et al. Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy. J Biomech. 2003; 36:1009-1017.
[62] Andersen H, Gjerstad MD, Jakobsen J. Atrophy of foot muscles: a measure of diabetic neuropathy. Diabetes Care. 2004; 27:2382-2385.
[63] Bus SA, Maas M, Cavanagh PR, Michels RP, Levi M. Plantar fat-pad displacement in neuropathic diabetic patients with toe deformity: a magnetic resonance imaging study. Diabetes Care. 2004; 27:2376-2381.
[64] Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. Am J Surg. 2004; 187:17S-24S.
[65] Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med. 1994; 331:854-860.
[66] Armstrong DG, Lavery LA. Elevated peak plantar pressures in patients who have Charcot arthropathy. J Bone Joint Surg Am. 1998; 80:365-369.
[67] Frykberg RG. Charcot arthropathy: pathogenesis and management. Wounds. 2000; 12(6 Suppl B): 35B-42B.
[68] Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Predictive value of foot pressure assessment as part of a population based diabetes

disease management program. Diabetes Care. 2003; 26:1069-1073
[69] Cavanagh PR, Ulbrecht JS, Caputo GM. New developments in the biomechanics of the diabetic foot. Diabetes Metab Res Rev. 2000; S6-S10.
[70] Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM. Preventive foot care in people with diabetes. Diabetes Care. 1998; 21:2161-2177.
[71] Murray HJ, Young MJ, Hollis S, Boulton AJ. The association between callus formation, high pressures and neuropathy in diabetic foot ulceration. Diabetic
[72] Med. 1996; 13:979-982.
[73] Young MJ, Cavanagh PR, Thomas G, Johnson MM, Murray H, Boulton AJ. The effect of callus removal on dynamic plantar foot pressures in diabetic patients. Diabet Med. 1992; 9:55-57.
[74] Armstrong DG, Lavery LA, Holtz-Neiderer K, Mohler MJ, Wendel CS, Nixon BP, et al. Variability in activity may precede diabetic foot ulceration. Diabetes Care. 2004; 27:1980-1984.
[75] Apelqvist J, Larsson J, Agardh CD. The influence of external precipitating factors and peripheral neuropathy on the development and outcome of diabetic foot ulcers. J Diabet Complications. 1990; 4:21-25.
[76] Uccioli L, Faglia E, Monticone G, Favales F, Durola L, Aldeghi A, et al. Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes Care. 1995; 18:1376-1378.
[77] Pecoraro RE. Chronology and determinants of tissue repair in diabetic lower extremity ulcers. Diabetes. 1991; 40:1305-1313.
[78] Gibbons GW. Lower extremity bypass in patients with diabetic foot ulcers. Surg Clin North Am. 2003; 83:659-669.
[79] Sumpio BE, Lee T, Blume PA. Vascular evaluation and arterial reconstruction of the diabetic foot. Clin Podiatr Med Surg. 2003; 20:689-708.
[80] International Working Group on the Diabetic Foot. International Consensus on the Diabetic Foot, edited by J Apelqvist, K Bakker, WH Van Houtum, MH Nabuurs-Franssen, and NC Schaper. Vol. 2005. International Working Group on the Diabetic Foot, Maatricht, 1999; 1036–1042.
[81] Mills JLBW, Taylor SM. The diabetic foot: Consequences of delayed treatment and referral. So Med J. 1991; 84:970
[82] Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. Diabetes Care.1991; 14:8-11.
[83] Boulton AJM. The pathway to ulceration. In: Boulton AJM, Connor H, Cavanagh PR editor. The Foot in Diabetes. 3rd ed. Chichester, UK: John Wiley and Sons; 2000;p. 19-31.
[84] Mueller MJ, Diamond JE, Delitto A, Sinacore DR. Insensitivity, limited joint mobility, and plantar ulcers in patients with diabetes mellitus. Physical Therapy. 1989; 69:453-462.
[85] Brownlee M. Glycation products and the pathogenesis of diabetic complications. Diabetes Care. 1992; 15:1835-1843.
[86] Delbridge L, Perry P, Marr S, Arnold N, Yue DK, Turtle JR, et al. Limited joint mobility in the diabetic foot: relationship to neuropathic ulceration. Diabet Med. 1988; 5:333-337.
[87] Zimny S, Schatz H, Pfohl M. The role of limited joint mobility in diabetic patients with an at-risk foot. Diabetes Care. 2004; 27:942-946.
[88] Grant WP, Foreman EJ, Wilson AS, Jacobus DA, Kukla RM. Evaluation of Young's modulus in Achilles tendons with diabetic neuroarthropathy. J Am Podiatr Med Assoc. 2005; 95:242-246.
[89] Grant WP, Sullivan R, Soenshine DE, Adam M, Slusser JH, Carson KA, et al. Electron microscopic investigation of the effects of diabetes mellitus on the achilles tendon. J Foot Ankle Surg. 1997; 36:272-278.
[90] Frykberg RG. Diabetic foot ulcerations: management and adjunctive therapy. Clin Podiatr Med Surg. 2003; 20:709-728.
[91] Abouaesha F, van Schie CH, Armstrong DG, Boulton AJ. Plantar soft-tissue thickness predicts high peak plantar pressure in the diabetic foot. J Am Podiatr Med Assoc. 2004; 94:3942.
[92] Abouaesha F, van Schie CH, Griffths GD, Young RJ, Boulton AJ. Plantar tissue thickness is related to peak plantar pressure in the high-risk diabetic foot. Diabetes Care. 2001; 24:1270-1274.
[93] D'Ambrogi E, Giurato L, D'Agostino MA, Giacomozzi C, Macellari V, Caselli A, et al. Contribution of plantar fascia to the increased forefoot pressures in diabetic patients. Diabetes Care. 2003; 26:1525-1529.
[94] D'Ambrogi E, Giacomozzi C, Macellari V, Uccioli L. Abnormal foot function in diabetic patients: the altered onset of Windlass mechanism. Diabet Med. 2005; 22:1713-1719.
[95] Piaggesi A, Romanelli M, Schipani E, Campi F, Magliaro A, Baccetti F, et al. Hardness of plantar skin in diabetic neuropathic feet. J Diabetes Complications. 1999; 13:129-134.
[96] Ahroni JH , Boyko EJ , Forsberg RC. Clinical correlates of plantar pressure among diabetic veterans. Diabetes Care. 1999; 22:965-972.
[97] Rathur HM, Boulton AJ. Pathogenesis of foot ulcers and the need for offloading. Horm Metab Res. 2005; 37: 61-68.
[98] Brand PW. Repetitive stress in the development of diabetic foot ulcers. In: Levin ME, Davidson JK editor. The Diabetic Foot. 4th ed. St Louis: Mosby;1988;p. 83-90.
[99] Habershaw G, Chrzan JS. Biomechanical considerations of the diabetic foot. In: Kozak GP, Campbell DR, Frykberg RG, Habershaw GM editor. Management of Diabetic Foot Problems. 2nd ed. Philadelphia: WB Saunders; 1995;p. 53-65
[100] Lavery LA, Armstrong DG, Wunderlich RP, Tredwell JL, Boulton AJM. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. Diabetes Care. 2003; 26:1069-1073.
[101] Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care. 2000; 23:606-611.

[102] Armstrong DG , Peters EJ , Athanasiou KA , Lavery LA. Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? J Foot Ankle Surg. 1998; 37:303-307.
[103] Armstrong DG, Lavery LA. Plantar pressures are higher in diabetic patients following partial foot amputation. Ostomy Wound Manage. 1998; 44:30-32 34,36.
[104] Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003; 26:510-513.
[105] Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care. 2003; 26:1435-1438.
[106] Armstrong DG , Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound Journal. 2004; 1:123-132.
[107] Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. Diabetes Metab Res Rev. 2004; 20:S68-S77.
[108] Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004; 39:885-910.
[109] Caputo GM. The rational use of antimicrobial agents in diabetic foot infection. In: Boulton AJM, Connor H, Cavanagh PR editor. The Foot in Diabetes. 3rd ed. Chichester: Wiley and Sons; 1994;p 143-151.
[110] Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. J Diabetes Complications. 1999; 13:254-263.
[111] Jeffcoate WJ , van Houtum WH. Amputation as a marker of the quality of foot care in diabetes. Diabetologia. 2004; 47:2051-2058.
[112] Resnick HE, Carter EA, Sosenko JM, Henly SJ, Fabsitz RR, Ness FK, et al. Incidence of lower-extremity amputation in American Indians: the Strong Heart Study. Diabetes Care. 2004; 27:1885-1891.
[113] Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. Diabetes Care. 2003; 26:491-494.
[114] Hennis AJ, Fraser HS, Jonnalagadda R, Fuller J, Chaturvedi N. Explanations for the high risk of diabetes-related amputation in a Caribbean population of black african descent and potential for prevention. Diabetes Care. 2004; 27:2636-2641.
[115] Frykberg RG. An evidence-based approach to diabetic foot infections. Am J Surg. 2003; 186:44S-54S
[116] UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes
[117] (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352:854-865.
[118] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependant diabetes mellitus. N Engl J Med. 1993; 329:966-986.
[119] American Diabetes Association. Implications of the Diabetes Control and Complications Trial. Diabetes Care. 2000; 23: S24-S26.
[120] American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. Diabetes Care. 2000; 23: S27-S31. 119. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Risk factors predicting lower extremity amputations in patients with NIDDM. Diabetes Care. 1996; 19:607-612.
[121] Humphrey AR, Dowse GK, Thoma K, Zimmet PZ. Diabetes and nontraumatic lower extremity amputations. Incidence, risk factors, and prevention a 12-year follow-up study in Nauru. Diabetes Care. 1996; 19:710-714.
[122] Driver VR, Madsen J, Goodman RA. Reducing amputation rates in patients with diabetes at a military medical center: the limb preservation service model. Diabetes Care. 2005; 28:248-253.
[123] Van Gils CC, Wheeler LA, Mellstrom M, Brinton EA, Mason S, Wheeler CG. Amputation prevention by vascular surgery and podiatry collaboration in high-risk diabetic and nondiabetic patients. The Operation Desert Foot experience. Diabetes Care. 1999; 22:678-683.
[124] Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Heagerty PJ. Prediction of diabetic foot ulcer using readily available clinical information: the Seattle Diabetic Foot Study. Diabetes. 2002; 51:18, last page.
[125] Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. J Intern Med. 1993; 233:485-491.
[126] Aulivola B, Hile CN, Hamdan AD, Sheahan MG, Veraldi JR, Skillman JJ, et al. Major lower extremity amputation: outcome of a modern series. Arch Surg. 2004; 139:395-399.
[127] Bodily KC, Burgess EM. Contralateral limb and patient survival after leg amputation. Am J Surg. 1983; 146:280-282.
[128] Collins KA, Sumpio BE. Vascular assessment. Clin Podiatr Med Surg. 2000;17:171-191.
[129] Akbari CM, Sidawy AN. Overview of the Diabetic Foot and Limb Salvage. In: Sidawy AN editors. Diabetic Foot: Lower Extremity Arterial Disease and Limb Salvage. Philadelphia: Lippincott Williams & Wilkins; 2006;p. 1-10.
[130] Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA. 1995; 273:721-723.
[131] Lipsky BA. Medical treatment of diabetic foot infections. Clin Infect Dis. 2004;39:S104-S114.
[132] Young MJ. Classification of ulcers and its relevance to management. In:Boulton AJM , Connor H , Cavanagh PR editor. The Foot in Diabetes. 3rd ed. Chichester: John Wiley and Sons; 2000;p. 61-72.
[133] Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998; 21:855-859.
[134] Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A comparison of two

diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care. 2001; 24:84-88.
[135] Wagner FW. The dysvascular foot: a system for diagnosis and treatment. Foot and Ankle.1981; 2:64-122.
[136] Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care.1998; 21:855-859.
[137] Schaper NC. Diabetic foot ulcer classification system for research purposes: A progress reports on criteria for including patients in research studies. Diabetes Metab Res Rev. 2004; 20:S90-S95
[138] Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev. 2004; 20:S90-S95.
[139] Markowitz JS, Gutterman EM, Magee G, Margolis DJ. Risk of amputation in patients with diabetic foot ulcers: a claims-based study. Wound Repair Regen.2006; 14:11-17.
[140] Patout CA, Birke JA, Horswell R, Williams D, Cerise FP. Effectiveness of comprehensive diabetes lower-extremity amputation prevention program in a predominantly low-income African American population. Diabetes Care. 2000; 23:1339-1342.
[141] Ollendorf DA, Kotsanos JG, Wishner WJ, Friedman M, Cooper T, Bittoni M, et al. Potential economic benefits of lower-extremity amputation prevention strategies in diabetes. Diabetes Care. 1998; 21:1240-1245.
[142] Apelqvist J, Ragnarson-Tennvall G, Larsson J, Persson U. Long-term costs for foot ulcers in diabetic patients in a multidisciplinary setting. Foot Ankle Int. 1995;16:388-394.
[143] Wraight PR, Lawrence SM, Campbell DA, Colman PG. Creation of a multidisciplinary, evidence based, clinical guideline for the assessment, investigation and management of acute diabetes related foot complications. Diabet Med. 2005; 22:127-136.
[144] Driver VR. Silver dressings in clinical practice. Ostomy Wound Manage. 2004; 50:11S-15S. .
[145] Gibbons GW, Marcaccio EJ, Burgess AM, Pomposelli FB, Freeman DV, Campbell DR, et al. Improved quality of diabetic foot care, 1984 vs. 1990. Reduced length of stay and costs, insufficient reimbursement. Arch Surg. 1993;128:576-581.
[146] Aulivola B, Pomposelli FB. Dorsalis pedis, tarsal and plantar artery bypass. J Cardiovascular Surg (Torino). 2004; 45:203-212.
[147] Pomposelli FB, Kansal N, Hamdan AD, Belfield A, Sheahan M, Campbell DR, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. J Vasc Surg. 2003; 37:307-315.
[148] Cook SD, Ryaby JP, McCabe J, Frey JJ, Heckman JD, Kristiansen TK. Acceleration of tibia and distal radius fracture healing in patients who smoke. Clin Orthop Relat Res. 1997; 337:198-207.
[149] Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005;366:1736-1743
[150] Lobmann R, Schultz G, Lehnert H. Proteases and the diabetic foot syndrome:mechanisms and therapeutic implications. Diabetes Care. 2005; 28:461-471
[151] Mulder GD, Vande Berg JS. Cellular senescence and matrix metallo proteinase activity in chronic wounds. Relevance to debridement and new technologies. JAm Podiatr Med Assoc. 2002; 92:34-37.
[152] Driver VR, Landowski M, Madsen J. The diabetic foot: from assessment to treatment. In: Bryant R editors. Acute and Chronic Wounds: Nursing Management. 3rd ed. St. Louis: Mosby; 2004;p. 307-336.
[153] Silverstein P. Smoking and wound healing. Am J Med. 1992; 93:22S-24S.
[154] Vileikyte L, Peyrot M, Bundy C, Rubin RR, Leventhal H, Mora P, et al. The development and validation of a neuropathy and foot ulcer-specific quality of life instrument. Diabetes Care. 2003; 26:2549-2555.
[155] Vileikyte L, Rubin RR, Leventhal H. Psychological aspects of diabetic neuropathic foot complications: an overview. Diabetes Metab Res Rev. 2004; 20:S13-S18.
[156] Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005; 366:1736-1743.
[157] Falanga V. Wound bed preparation: science applied to practice. European Wound Management Association (EWMA). Position Document: Wound Bed Preparation in Practice2004; p 2-5.
[158] Bowering CK. Diabetic foot ulcers. Pathophysiology, assessment, and therapy. Can Fam Physician. 2001; 47:1007-1016.
[159] Enoch S, Harding K. Wound bed preparation: the science behind the removal of barrier to healing. Wounds. 2003; 15:213-229.
[160] Edmonds M, Foster A, Vowden P. Wound bed preparation for diabetic foot ulcers. European Wound Management Association (EWMA). Position Document: Wound Bed Preparation in Practice, 2004; p 6-11.
[161] Miller M. The role of debridement in wound healing. Community Nurse. 1996; 2:52-55.
[162] Levin M. Diabetic foot wounds: pathogenesis and management. Adv WoundCare. 1997; 10:24-30.
[163] Sieggreen MY, Maklebust J. Debridement: choices and challenges. Adv Wound Care. 1997; 10:32-37.
[164] Driver VR. Treating the macro and micro wound environment of the diabetic patient: managing the whole patient, not the hole in the patient. Foot and Ankle Quarterly The Seminar Journal. 2004; 16:47-56.
[165] Steed D. Modulating wound healing in diabetes. In: Bowker J, Pfeiffer M editor. Levin and O'Neal's The Diabetic Foot. St. Louis: Mosby; 2001;p. 395-404.
[166] Attinger CE, Bulan E, Blume PA. Surgical debridement: the key to successful wound healing and reconstruction. Clin Podiatr Med Surg. 2000; 17:599-630.
[167] Falanga V. Wound bed preparation and the role of enzymes: a case for multiple actions of therapeutic agents. Wounds. 2002; 14:47-57.
[168] Jung W, Winter H. Considerations for the use of Clostridial collagenase in clinical practice. Clin Drug Invest. 1998; 15:245-252.

[169] Drager E, Winter H. Surgical debridement versus enzymatic debridement. In: Baharestani M, Gottrup F, Holstein P, Vanscheidt W editor. The Clinical Relevance of Debridement. New York: Springer Verlag; 1999;p. 59-71.
[170] Ayello E, Cuddigan J. Debridement: controlling the necrotic/cellular burden. Adv Skin Wound Care. 2004; 17:66-75.
[171] Alvarez OM, Fernandez-Obregon A, Rogers RS, Bergamo L, Masso J, Black M. A prospective, randomized, comparative study of collagenase and papain-urea for pressure ulcer debridement. Wounds. 2002; 14:293-301.
[172] Eaglstein WH, Falanga V. Chronic wounds. Surg Clin North Am. 1997; 77:689-700.
[173] Scott RG, Loehne HB. 5 questions and answers about pulsed lavage. Adv Skin Wound Care. 2000; 13:133-134.
[174] Armstrong DG, Mossel J, Short B. Age of diabetic foot and ankle wounds. J Wound Care 14; 1998:173-176.
[175] Armstrong DG, Mossel J, Short B, Nixon BP, Knowles EA, Boulton AJ. Maggot debridement therapy: a primer. J Am Podiatr Med Assoc. 2002; 92:398-401.
[176] Mumcuoglu KY. Clinical applications for maggots in wound care. Am J Clin Dermatol. 2001; 2:219-227.
[177] Sherman RA. Maggot therapy for foot and leg wounds. Int J Low Extrem Wounds. 2002; 1:135-142.
[178] Sherman RA. Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. Diabetes Care. 2003; 26:446-451.
[179] Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature. 1962; 193:293-294.
[180] Falanga V. Classifications for wound bed preparation and stimulation of chronic wounds. Wound Repair Regen. 2000; 8:347-352.
[181] Hansson C. Interactive wound dressings. A practical guide to their use in older patients. Drugs Aging. 1997; 11:271-284.
[182] Dinh T, Pham H, Veves A. Emerging treatments in diabetic wound care. Wounds.2002; 14:2-10.
[183] Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs. standard treatment in the management of diabetic foot ulcers. Arch Surg. 2002; 137:822-827.
[184] Ovington LG. Overview of matrix metalloprotease modulation and growth factor protection in wound healing. Part 1. Ostomy Wound Manage. 2002; 48: 3-7.
[185] Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet. 2003; 361:1545-1551.
[186] Mulder G, Armstrong DG, Seaman S. Standard appropriate and advanced care: medical legal considerations for diabetic lower extremity wounds. Wounds. 2003; 26:1069-1073.
[187] Wieman TJ. Clinical efficacy of becaplermin (rhPDGF-BB) gel. Becaplermin Gel Studies Group. Am J Surg. 1998; 176: 74S-79S.
[188] Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care. 1998; 21:822-827.
[189] Li V, Kung E, Li W. Molecular therapies for wounds: modalities for stimulating angiogenesis and granulation. In: Lee B editors. The Wound Management Manual. New York: McGraw-Hill; 2005;p. 17-43.
[190] Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL. Classification and treatment of chronic nonhealing wounds: successful treatment with autologous platelet-derived wound healing factors (PDWHF). Ann Surg. 1986; 204:330-332.
[191] Falanga V, Shen J. Growth factors, signal transduction and cellular responses. In: Falanga V editors. Cutaneous Wound Healing. London: Martin Dunitz Ltd; 2001;p. 81-93.
[192] Robson M, Smith P. Topical use of growth factors to enhance healing. In:Falanga V editors. Cutaneous Wound Healing. London: Martin Dunitz Ltd; 2001;p. 379-398.
[193] Hogge J, Krasner D, Nguyen HC, Harkless LB, Armstrong DG. The potential benefits of advanced therapeutic modalities in the treatment of diabetic foot wounds. J Am Podiatr Med Assoc. 2000; 90:57-65.
[194] Margolis DJ , Kantor J , Santanna J , Strom BL , Berlin JA. Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. Diabetes Care. 2001; 24:483-488.
[195] Brigido S. Healing Debilitating Diabetic Foot Ulcers. Orthopedic Technology Review. The diabetic foot. Br J2004; 6(6): 382, last page.
[196] Cianci P. Advances in the treatment of the diabetic foot: is there a role for adjunctive hyperbaric oxygen therapy? Wound Repair Regen. 2004; 12:2-10.
[197] Kranke P, Bennett M, Roeckl-Wiedmann I. Hyperbaric oxygen therapy for chronic wounds (Cochrane Review). Cochrane Database Syst Rev. 2003; 2: 125-126.
[198] Niinikoski J. Hyperbaric oxygen therapy of diabetic foot ulcers, tran scutaneous oxymetry in clinical decision-making. Wound Repair Regen. 2003; 11:458-461.
[199] Strauss MB. Hyperbaric oxygen as an intervention for managing wound hypoxia: its role and usefulness in diabetic foot wounds. Foot Ankle Int. 2005; 26:15-18.
[200] Wunderlich RP, Peters EJ, Lavery LA. Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot. Diabetes Care. 2000; 23:1551-1555.
[201] O'Meara S, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. Health Technol Assess. 2000; 4:1-237.
[202] Ennis WJ, Foremann P, Mozen N, Massey J, Conner-Kerr T, Meneses P. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Manage. 2005;51:24-39.
[203] Thawer HA, Houghton PE. Effects of ultrasound delivered through a mist of saline to wounds in mice

with diabetes mellitus. J Wound Care. 2004; 13:171-176.
[204] Torke K. Healing wounds through ultrasound. Podiatry Management. Nov-Dec 2004; 130-134.
[205] Armstrong DG, Attinger CE, Boulton AJ, Frykberg RG, Kirsner RS, Lavery LA, et al. Guidelines regarding negative wound therapy (NPWT) in the diabetic foot. Ostomy Wound Manage. 2004; 50: 3S-27S.
[206] Armstrong DG, Lavery LA, Abu-Rumman P, Espensen EH, Vazquez JR,Nixon BP, et al. Outcomes of subatmospheric pressure dressing therapy on wounds of the diabetic foot. Ostomy Wound Manage. 2002; 48:64-68.
[207] DeFranzo AJ, Argenta LC, Marks MW, Molnar JA, David LR, Webb LX, et al. The use of vacuum-assisted closure therapy for the treatment of lower-extremity wounds with exposed bone. Plast Reconstr Surg. 2001; 108:1184-1191.
[208] Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997; 38:553-562.
[209] Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation. Ann Plast Surg. 2003; 51:210-218.
[210] Niezgoda JA, Schibly B. Negative-pressure wound therapy (vacuum assisted closure). In: Lee B editors. The Wound Management Manual. New York: McGraw-Hill; 2005;p. 65-71.
[211] Saltzman CL. Salvage of diffuse ankle osteomyelitis by single-stage resection and circumferential frame compression arthrodesis. Iowa Orthop J. 2005; 25:47-52.211. Webb LX. New techniques in wound management: vacuum-assisted wound closure. J Am Acad Orthop Surg. 2002; 10:303-311.
[212] Yuan-Innes MJ, Temple CL, Lacey MS. Vacuum-assisted wound closure: a new approach to spinal wounds with exposed hardware. Spine. 2001; 26:30-33.
[213] Scherer LA, Shiver S, Chang M, Meredith JW, Owings JT. The vacuum assisted closure device: a method of securing skin grafts and improving graft survival. Arch Surg. 2002; 137:930-933.
[214] Venturi ML, Attinger CE, Mesbahi AN, Hess CL, Graw KS. Mechanisms and clinical applications of the vacuum-assisted closure (VAC) device: a review. Am J Clin Dermatol. 2005; 6:185-194.
[215] Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005; 366:1704-1710.
[216] McCulloch JM. Electrical Stimulation in Wound Repair. In: Lee B editors. The Wound Management Manual. NewYork: McGraw Hill; 2005;p. 80-89.
[217] Lundeberg TCM, Eriksson V, Malm M. Electrical nerve stimulation improves healing of diabetic ulcers. Annals of Plastic Surgery. 1992; 29:328-331.
[218] Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJM, Harkless LB. Offloading the diabetic foot wound: a randomized clinical trial. Diabetes Care. 2001; 24:1019-1022.
[219] Armstrong DG, Lavery LA, Nixon BP, Boulton AJM. It is not what you put on, but what you take off: techniques for debriding and offloading the diabetic foot wound. Clin Infect Dis. 2004; 39:S92-S99.
[220] Brem H, Sheehan P, Boulton AJ. Protocol for treatment of diabetic foot ulcers. Am J Surg. 2004; 187:1S-10S.
[221] Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care. 2005; 28:551-554.
[222] Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005; 366:1725-1735.
[223] Zimny S, Schatz H, Pfohl U. The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers. Diabet Med. 2003; 20:622-625.
[224] Birke JA, Pavich MA, Patout CA, Horswell R. Comparison of forefoot ulcer healing using alternative off-loading methods in patients with diabetes mellitus. Adv Skin Wound Care. 2002; 15:210-215.
[225] Zimny S, Reinsch B, Schatz H, Pfohl M. Effects of felted foam on plantar pressures in the treatment of neuropathic diabetic foot ulcers. Diabetes Care. 2001; 24:2153-2154.
[226] Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable offloading devices in the management of neuropathic diabetic foot ulcers. Diabetes Care. 2005; 28:555-559.
[227] Bailey & love's 24 edition Chapter 15 'Cysts, Ulcers and Sinuses by Olagunju A. Ogunbiyi page no 209-15.3 box.
[228] Bailey & love's 24 Edition Chapter 15 'Cysts, Ulcers and Sinuses by Olagunju A.Ogunbiyi page no 209
[229] Biomaterials Volume 21, Issue 17, September 2000, Pages 1797-1802
[230] Woodley DT. In:clack RAF, ed. The molecular and cellular biology of wound repair. 2nd Ed. New york: Plenum, 1996:339-54.
[231] Bennet N, Schultz G. Growth factors and wound healing: biochemical properties of growth factors and their receptors. Am J Surg 1993; 165:728-737.
[232] Nanney LB, King LE Jr In:clark RAF, ed The molecular and cellular Biology of wound repair. 2nd Ed. New york: plenum, 1996:171-94.
[233] Werner S, Smola H, Liao X, Longaker M, Krieg T, Hosfschneider PH, Williams L. The function of KGF in morphogenesis of epithelium and reepithelialization of wounds. Science 1994; 266:819-22.
[234] Brown Gl, nanney LB, Griffen J, crerner Ab, yancey JM, Curtsinger LJ, Holtzin L, Schultz GS, Jurkiewicz Mj, Lynch JB. Enhancement of wound healing by topical treatment with epidermanl growth factor. N Engl J Med 1989; 321:76-79.
[235] Peppelenbosch MP, Tertoolen LG, Hage W J, de Laat SW. Epidermal growth factor-induced actin remodeling is regulated by 5-lipoxygenase and

cyclooxygenase products. Cell 1993; 74: 565-75.
[236] Barrandon Y, Green H.Cell migration is essential for sustained growth of keratinocyte colonies: the roles of transforming growth factor-alpha and epidermal growth factor. Cell 1987; 50:1131-37.
[237] Ellis Dl Kafka S, chow J, Nanney LB, lnman W, Mc Cadden M, king LE. Melanoma, Growth factor, acanthosis nigricans, the sing of Leser- Trelat and multiple Acrochordons: A role for transforming growth factor-alpha in cutaneous paraneoplastic syndromes. N Engl J Med 1987; 317(25): 1582-87.
[238] Thomas S (2000a) Alginate dressings in surgery and wound management part I. Journal of Wound Care 9(2): 56-60
[239] Ng RW; Cheng YL Calcium alginate dressing-related hypercalcemia.J Burn Care Res. 2007; 28:203-4
[240] Pudner, 2001 Pudner R (2001) Alginate and hydrofibre dressings in wound management. Journal of Community Nursing 15(5): 38-42
[241] Belmin J, Meaume S, Rabus M, Bohbot S (2002) Sequential treatment with calcium alginate dressings and hydrocolloid dressings accelerates pressure ulcer healing in older subjects: a multicentre randomised trial of sequential versus non-sequential treatment with hydrocolloid dressings alone. Journal of the American Geriatric Society 50 (February): 269-74.
[242] Sayag MD, Meume S, Bohbot S (1996) Healing properties of calcium alginate dressings. Journal of Wound Care 5(8): 357-62.

Author Profile

Viswanath Nallapaneni, Associate Professor, Department of General surgery, Katuri Medical College, Katurinagar, chinakondrupadu, Guntur, Guntur Dt , PIN: 522019.