Overview of diabetic foot; novel treatments in diabetic foot ulcer

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ABSTRACT

Foot ulcers are one of the main complications in diabetes mellitus, with a 15% life time risk in all diabetic patients. The problem and features are infection, ulceration, or gangrene. Neuropathy, poor circulation, and susceptibility to infection are the three major contributors to the development of diabetic foot; which when present, foot deformities or minor trauma can readily lead to ulceration and infection. Not all diabetic foots are preventable, but appropriate preventive measures can dramatically reduce their occurrences. Awareness of physicians about foot problems in diabetic patients, clinical examination and Para clinical assessment, regular foot examination, patient education, simple hygienic practices and provision of appropriate footwear combined with prompt treatment of minor injuries can decrease ulcer occurrence by 50%. Many different methods have been proposed and their goal is to accelerate the wound healing. These treatments other than standard therapy include local use of epidermal growth factor, vacuum-compression therapy (VCT), hyperbaric oxygen and peripheral Stem cell injection. Since all these treatments have a partial effect in ulcer improvement and amputation rate; so more effective treatments are essential.

A novel drug for treatment of this complication is an herbal extract, ANGIPARS™, which has been studied in all steps of clinical trial. This new treatment by topical, oral and intravenous routs has had beneficial effects in the treatment of diabetic foot ulcer after one month. Angiogenesis is one of the considered mechanisms of action of this drug. Results of these clinical trials showed that this treatment can be superior to other treatments.

Keywords: Diabetic foot ulcer, Overview, Treatment, ANGIPARS™

INTRODUCTION

Diabetes is the most common metabolic disease worldwide. IDF and WHO reported increasing incidence all around the world especially in developing countries. Today about 2566000 people (6%) are suffering from diabetes and its complications in Iran. The prevalence of diabetes is increasing in Iran like other developing countries (1). Burden of diabetes mellitus in Iran is disproportionately expensive according to a study in 2001, disability adjusted life years (DALYs) for diabetes in Iran was 306,440 years and 4.72 years per 1000 people (2).

Foot ulcers are one of the main complications in diabetes mellitus and 15% of diabetic patients develop foot ulcer and 15-20% of these will require amputation (3). A retrospective study (between 1979-2001) in Tehran university of medical sciences determined that over the 22-year period of the study, 281 patients (61% men and 39% women) were hospitalized for diabetic foot ulcers. The overall lower limb amputation rate was 30%. Mean hospital stay was significantly longer in patients who eventually underwent amputation than in those who did not. The rate of lower limb amputation secondary to diabetic foot ulcer is higher in Iran than the global average (4).

Mean duration of hospital admission for diabetic foot was 4 weeks, amputation rate was 40% in 1995 and decreased to 14% in 2001(4, 5).

Survival of amputee patients' life expectancy following amputation was 4.32 years in a study (2). The cost of treatment of a simple ulcer in Iran is $5000 to $8000(6). Many different methods have been proposed for promotion of wound healing. Here we present a review of treatments of diabetic foot ulcer and introduce a new herbal extract for treatment of diabetic foot ulcers which has been studied and is being patented internationally.

PATHOGENESIS OF DIABETIC FOOT

The problem and features of diabetic foot are infection, ulceration, or gangrene. Neuropathy, poor circulation, and susceptibility to infection are the three major contributors to the development of diabetic foot; which when present, foot deformities or minor trauma can readily lead to ulceration and infection(3).
Diabetic Neuropathy

Diabetic neuropathy is the most common and troublesome complication of diabetes mellitus and it is the most common form of neuropathy in the developed countries. Diabetic neuropathy is responsible for 50-75% of non-traumatic amputations (7, 8). Neuropathy is present in more than 80% of patients with foot ulcers and increases the risk of amputation 1.7 fold; 12 fold, if there is deformity, and 36 fold, if there is a history of previous ulceration (9). Poor glycemic control and oxidative stress have important roles in diabetic complications. Binding of AGEs to their receptors can lead to modification in cell signaling and further production of free radicals. Metabolic and oxidative insults often cause rapid changes in glial cells and tend to neuropathy (10). Neuropathy results in decreasing pain sensation and perception of pressure, lack of autonomic tone in the capillary and shunting of blood from arteries into veins. Foot feels warm and distended veins and bounding pulses (11). Sensory, motor and autonomic neuropathies are predisposing factors. In a case-control study in Iran, 110 diabetic patients were evaluated for potential risk factors for diabetic neuropathy. Statistically significant relationships were found between neuropathy and age, gender, quality of diabetes control and duration of disease. No correlation was found with any atherosclerosis risk factors (high BP, hyperlipidemia, cigarette smoking) (12). Mechanical (shoe), thermal and chemical trauma are the usual precipitating events. Injured tissues are very sensitive to secondary infections. Peripheral arterial disease: Arterial disease in diabetics is often both macrovascular and microvascular. Limb-threatening ischemia is most often seen when two or more levels of the distal arterial tree have either significant stenoses or occlusions. Peripheral arterial disease reduces the blood supply needed for healing of ulcers and infections. This most often involves aortoiliac and femoropopliteal segments or femoropopliteal and tibial segments (13).

Susceptibility to Infection

Patients with diabetes mellitus (DM) are prone to infection, in part due to phagocyte dysfunction and impaired polymorphonuclear (PMN) leucocyte superoxide generation. Another frequently mentioned factor in the pathogenesis of infection in DM patients is altered zinc status. We have evaluated the association between serum zinc level and PMN respiratory burst activity in patients with type 2 DM. A significant negative correlation between serum zinc level and nitro blue tetrazolium (NBT) index at baseline was seen in patients with foot ulcers, but this changed to a significant positive correlation after stimulation. These findings may be explained by PMN hyperactivity at baseline and by respiratory burst dysfunction following stimulation in diabetic patients (14).

PREVENTION AND TREATMENT OF ULCERS

Not all diabetic foots are preventable, but appropriate preventive measures can dramatically reduce their occurrences. Awareness of physicians about foot problems in diabetic patients, clinical examination and Para clinical assessment, regular foot examination, patient education, simple hygienic practices and provision of appropriate footwear combined with prompt treatment of minor injuries can decrease ulcer occurrence by 50%(6). Many different methods have been proposed and their goal is to accelerate the wound healing.

Acceleration the Wound Healing

Basic principles of wound healing include appropriately treated infection, adequate arterial inflow and off loading or removing pressure from the wound.

Control of infection

After classification of ulcers, proper antimicrobial therapy should be done for infective ulcers. Treatment of osteomyelitis and appropriate debridement are necessary. A number of small trials have evaluated the possible efficacy of granulocyte colony-stimulating factor in diabetics with foot infections (15-18). A meta-analysis was performed on five trials with a total of 167 patients (19). Although adjunctive G-CSF did not appear to hasten the clinical resolution of infection or ulceration, it reduced the rate of surgical procedures including amputation (relative risk 0.41, CI 95% 0.17-0.95).

Method of debridement

The method of debridement may also be important. Various types of products have been used to keep the wound dry and covered (hydrogels, hydrocolloids, alginates and foams) (20). In a systematic review, hydrogels were significantly more effective than gauze or standard care in healing foot ulcers among diabetic patients (21). Larval therapy showed no significant benefit in small size studies. Clinical trials of enzyme preparations and polysaccharide beads are not yet available (11).

Off loading

Total contact casts and therapeutic shoes are proper options for removal of pressure from the wound.
Revascularization
Adequate arterial inflow plays an important role in the management of diabetic foot ulcers in patients with documented peripheral arterial disease. The efficacy of this approach was evaluated in a report for 29 diabetic patients who underwent percutaneous transluminal angioplasty followed by therapy with aspirin and warfarin (22). This study sought to determine whether infrapopliteal transcatheter interventions can salvage ischemic limbs in diabetic patients referred for below the knee amputation. At 12 month follow-up, 23 had experienced wound healing and avoided below the knee amputation. The tissue oxygen partial pressure levels improved in all patients who eventually had healed and healing ulcers, in contrast to the ankle-brachial index, served as a useful predictor of outcome.

Topical Agents for Treatment of Diabetic Foot Ulcer

Platelet-derived growth factor
A platelet-derived growth factor gel preparation (Becaplermin) is approved by the US Food and Drug Administration as an adjuvant therapy for diabetic foot ulcers (23).

Epidermal Growth Factor
In addition, local application of human epidermal growth factor may promote healing of diabetic foot ulcers (24). Results of one clinical trial revealed that administration of Epidermal Growth Factor (EGF) resulted in statistically significant wound closure in comparison to placebo (25). After 4 weeks, mean closure was significantly higher in EGF group compared with placebo (71.2% vs. 48.9%, P<0.03). 100% closure was observed in 7 patients (With 30 ulcers) from EGF group and in one patient (With 12 ulcers) from placebo group. EGF showed a greater efficacy in ulcer healing (RR=3.4, 95%CI: 1.84-13.61).

Tretinoin
The use of tretinoin solution for 10 minutes a day followed by iodine gel for four weeks resulted in complete resolution of 46% of the ulcers in the treatment group (n = 13) compared to 18 % in control group (n = 11) (26).

Human skin equivalents
Human skin equivalents in noninfected, nonischemic regions may be used. In one study of 208 patients, application of the cultured skin equivalent (Graftskin®) for 4 weeks improved the healing rate (27).

Topical and systemic hyperbaric oxygen
The effect of 2 weeks of topical hyperbaric oxygen (THO) treatment on the healing of diabetic foot ulcers without associated gangrene was evaluated in a prospective, controlled, and randomized manner in 28 patients (28). Ulcer size changes did not differ statistically between the controls and THO groups. A trend toward slower healing was observed in the THO group. Healing of diabetic foot ulcers was not accelerated by THO in this study. In a randomized trial of systemic hyperbaric oxygen therapy in 70 patients with severely ischemic foot ulcers (Wagner grades 3 and 4), the amputation rate was 9% in the treatment group and 33% in the control group (29).

Phenytoin
The efficacy of topical phenytoin in the treatment of diabetic foot ulcers was evaluated in a controlled inpatient study. Mean time to complete healing was 21 days with phenytoin and 45 days in control. The observed differences were statistically significant (P < 0.05). Phenytoin appears to be useful as a topical agent in promoting the healing of diabetic foot ulcers (30).

Compression Vacuum Therapy
A single-blind, randomized controlled trial was conducted to evaluate vacuum-compression therapy (VCT) for the healing of diabetic foot ulcers. The experimental group received VCT 1 hour a day, 4 times a week, for 10 sessions [(-75 mmHg) of negative pressure for 60 s, followed by (38.5 mmHg) of positive pressure for 30 s]. The experimental group significantly improved in measures of foot ulcer surface area compared with the control group (p = 0.024). Researchers believe that VCT systems do improve total tissue blood flow and oxygenation (31). In a retrospective study of payer claims data, patients with diabetic foot ulcers in the medicare sample treated with negative-pressure wound therapy had a lower incidence of amputations than those undergoing traditional wound therapy; this finding was evident in wounds of varying depths in both studied populations (32).

Other Topical therapies
In a trial electrical stimulation, given daily with a short pulsed, asymmetric biphasic waveform, was effective for enhancement of healing rates for patients with diabetes and open ulcers (33). The semipermeable polymeric membrane dressing and Derma graft are useful therapeutic options for treatment uncomplicated chronic diabetic foot ulcers (34, 35).
The other new therapies that have been studied in diabetic foot ulcer include: gene therapy, protease inhibitors, Angiogenesis stimulants, nitric oxide-releasing agents, adenosine agonists, immunostimulants, vasoactive compounds and granulating agents. These therapies should be considered when existing treatments have failed to heal ulceration in the diabetic foot (36).

A new Herbal Extract (ANGIPARS™)

As aforementioned noted, many different methods have been proposed to accelerate the wound healing in patients with diabetic foot ulcer. Most of these treatments have a partial effect in ulcer improvement and amputation rate; so more effective treatments are essential.

In preclinical studies toxicity effect of an herbal extract, Semelil (ANGIPARS™), which is considered for treatment of ulcer, is evaluated. In these experimental studies acute toxicity, genotoxicity (Comet assay), apoptotic effect, sub-acute Toxicity (In Rodents and Dogs), mutagenic properties (Ames test, dominant lethal mutation in germ cells, chromosomal aberration in bone marrow cells and DNA Damage by SOS-Chromotest), embryo toxic & teratogenic properties and allergic effects were evaluated. According to these studies, Semelil had no severe acute or chronic toxicity and it was recommended for clinical trials (37-39).

The Maximum Tolerated Dose (MTD) and Possible Dose Limiting Toxicities (DLTs) were determined. No toxicity or major side effects were observed up to daily dose of 10ml (40). Then the effects of herbal extract in diabetic foot ulcers were studied (41). A multicentric Clinical Trial for intravenous rout of this Herbal Extract was done and approval of efficacy in a larger scale randomized trial with more evidences on safety was evaluated. Semelil by intravenous rout is more effective than standard therapy without any side effects (42). Randomized controlled trials for oral and topical routs were done too (43). This herbal extract by oral, topical and combination of oral and topical rout is more effective than standard therapy without any side effects. This drug can be used in all types of diabetic ulcers. This new treatment decreased mean duration of hospital admission and its direct and indirect costs and decreased amputation rate in patients with diabetic foot ulcer. Angiogenesis is one of the considered mechanisms of action of Semelil. Results of these clinical trials showed that this treatment can be superior to other treatments.

CONCLUSION

Most of treatments of diabetic foot ulcer have a partial effect in ulcer improvement and amputation rate and some of the ulcers are retractable to conventional therapy; so more effective and cost benefit treatments are essential. Results of recent clinical trials showed that a new herbal extract, named ANGIPARS™, is very effective for treatment of foot ulcers and we suggest that this novel drug can be superior to other treatments and can be used in all types of ulcers.

REFERENCES


