# *Evaluation of stem cells in treatment of diabetic foot ulcers*

***Essay***

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# علاج قرح القدم السكرى بالخلايه الجذعية

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توطئة للحصول على درجة الماجستير في الجراحة العامة

مقدمه من الطبيبه


**رغدة السيد طلال توفيق**

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# *SUMMARY*

Recently it has been shown that careful glucose control can significantly decrease the complications of diabetes. Much effort has been expended to help diabetics maintain near-normal glucose levels. Those patients who have been successful have much better outcomes. For a variety of reasons, however, good blood glucose control is not easily obtained in a many patients. Therefore, the management of the complications is still a major focus of medical care, known that diabetic foot ulcers are common and serious complications of chronic diabetes mellitus.

Diabetic foot ulcers (DFUs) precede 85% of non traumatic lower extremity amputations (LEAs). Approximately 3-4% of individuals with diabetes currently have foot ulcers or deep infections. Among persons with diabetes, 15% develop foot ulcers during their lifetime. Their risk of LEA increases by a factor of 8 once an ulcer develops. At 2 years following transtibial amputation, 36% of these patients are known to have died.

Pathophysiologic factors involved in the development of diabetic foot ulcers are neuropathy, arterial insufficiency, musculoskeletal abnormalities, and poor wound healing. Microbial pathogens and poor nutrition also play a key role and compromise the healing process. The initiating injury may be from acute mechanical or thermal trauma or from repetitively or continuously applied mechanical stress.

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**Raghda El Sayed Tallal**

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# Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects of insulin secretion and/or increased cellular resistance to insulin. Chronic hyperglycemia and other metabolic disturbances of DM lead to long-term tissue and organ damage as well as dysfunction involving various body systems ***(Jerry C, 2009).***

The incidence of diabetes mellitus is increasing globally ***(Reiber G, 2001)***, and elder diabetics had twice the risk of developing a foot ulcer, three times the risk of developing a foot abscess and four times the risk of developing osteomyelitis ***(Reed J, 2004)***, Similarly diabetics are more prone to either local or higher amputations ***(Hall M and DeFrances C, 2003)***. In 2001, approximately$10.9 billion was spent on diabetic neuropathy and associated complications as foot ulcers, up to 27% of total medical costs of diabetes ***(Gordois A et al, 2003).***

Pathophysiologic factors involved in the development of diabetic foot ulcers are neuropathy, arterial insufficiency, musculoskeletal abnormalities, and poor wound healing. Microbial pathogens and poor nutrition also play a key role and compromise the healing process ***(Sumpio B, 2000).*** The initiating injury may be from acute mechanical or thermal trauma or from repetitively or continuously applied mechanical stress ***(Peter R et al, 2005)***.

The initial management of diabetic patients consists of proper foot care to prevent ulcers. Feet should be kept always clean and dry. Patients with neuropathy should not walk barefoot and properly fitted

shoes are essential. Glycemic control also is paramount in the prevention of diabetic neuropathy and the development of foot ulcers ***(Mark A and Arthur N et al, 2004).***

Management of diabetic ulcers includes cleansing of the wound, debridement of any necrotic or gangrenous foreign bodies or exposed bone ***(Garyson M et al, 1995)***, to reach a healthy base that will support granulation tissue and allow healing by secondary intention ***(Chen S et al, 2005)*.** Initial regimen of antimicrobial treatment should usually be selected empirically, and then be modified on the basis of both the patient's clinical response and the results of culture and sensitivity testing ***(Teppler H et al, 2000)***. Reconstructive surgery may also be indicated in patients with an unstable Charcot foot ***(Garapati R and Weinfeld S, 2004)***; however, many diabetic patients will need revascularisation to achieve timely and durable healing.

New treatments for diabetic foot ulcers continue to be introduced ***(Eldor R et al, 2004),*** yet few are subjected to controlled or comparative studies of their efficacy ***(Sibbald R and Mahoney J, 2003),*** including the use of negative pressure dressings ***(Armstrong D and Lavery L, 2005),*** hyperbaric oxygen treatment ***(Roeckl W et al, 2005),*** bioengineered skin equivalents ***(Scaap et al, 2004),*** growth-factor therapy ***(Smiell J et al, 1999,*** and bone-marrow-derived stem cells ***(Badiavas E et al, 2003).***

The concept of stem cells originated at the end of the 19th century as a theoretical postulate to account for the ability of certain tissues (blood, skin, etc.) to self-renew for the lifetime of an organism even though they are comprised of short-lived cells ***(Paolo B et al ,***

***2008)***. These are pluripotent cells in embryos ***(Jisun C and Vincent F, 2007)*** and can be isolated from normal blastocysts ***(Martin G, 1981***). Different types of stem cells could have different uses as in treatment of: Alzheimer's disease, Parkinsonism, degenerative conditions of bone and cartilage, and also for treatment of diabetic foot ulcers *(**Audrey R et al, 1999)***.

In treatment of diabetic foot ulcers the transplanted stem cells have the ability to migrate to the damaged tissue sites and stimulate repairs by differentiating into skin-specific cells. In addition, experiments of influence of local application of mesenchymal stem cells on cutaneous wound regeneration showing convertion into phenotypes of epidermal keratinocytes, sebaceous glands, follicular epithelial cells, and vascular endothelial cells by transdifferentiation ***(Fu X et al, 2007)***.

More general concerns regarding the use of stem cells, including the real risk of tumor formation following transplantation, also the wide array of social, political, legal, ethical, and economic issues must be considered ***(Bert V et al, 2001).*** yet we remain convinced that the field of stem cell biology holds tremendous promise for furthering our understanding of the human body and our ability to treat its maladies ***(Yu J et al, 2007).***

# Aim of the work

The aim of the work is to review the use of bone marrow derived stem cells in the treatment of diabetic foot ulcers as regards evolution, indications, results and limitations.

# ANATOMY OF THE FOOT

Knowledge of the anatomy of the foot is essential so that progression of disease in the diabetic foot can be understood and proper surgical treatment applied. Effective clinical evaluation and effective surgery are based on an understanding of the gross anatomy and of alterations produced by disease ***(klenerman et al, 2006).***

## I. Bones

There are three groups of bones in the foot:

- The seven tarsal bones, which form the skeletal framework for the ankle.
  - Metatarsals (I to V), There are five metatarsals in the foot, numbered I to V from medial to lateral. Metatarsal I, associated with the great toe, is shortest and thickest. The second is the longest. The plantar surface of the head of 1st metatarsal also articulates with two sesamoid bones. The sides of the bases of 2nd to 5th metatarsals also articulate with each other ***(Blevins C, 1994).***
- The phalanges, which are the bones of the toes-each toe has three phalanges, except for the great toe, which has two ***(Blevins C, 1994).***

### Tarsal bones

The tarsal bones are arranged in a proximal group and a distal group with an intermediate bone between the two groups on the medial side of the foot ***(Drake et al, 2004).***

### • Proximal group

The proximal group consists of two large bones, the talus (Latin for ankle) and the calcaneus (Latin for heel).

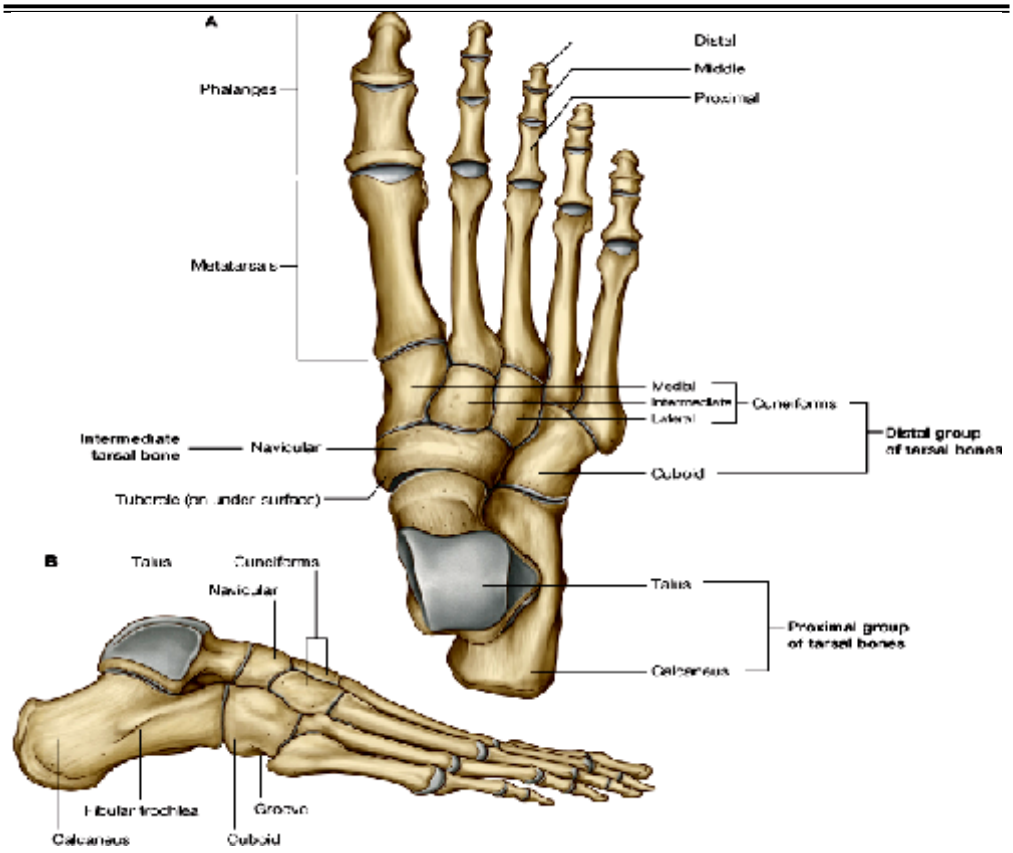


***Figure (1):*** Bones of the foot. **A.** Dorsal view, right foot. **B.** Lateral view, right foot ***(Drake et al, 2004).***

- **The intermediate tarsal bone**

On the medial side of the foot is the navicular (boat shaped). This bone articulates behind with the talus and articulates in front and on the lateral side with the distal group of tarsal bones ***(Chevallier A et al, 1977)***.

- **Distal group**

From lateral to medial, the distal group of tarsal bones consists of:

- The cuboid (Greek for cube).

- Three cuneiforms (Latin for wedge)-the lateral, intermediate, and medial cuneiform bones ***(Chevallier A et al, 1977)***.

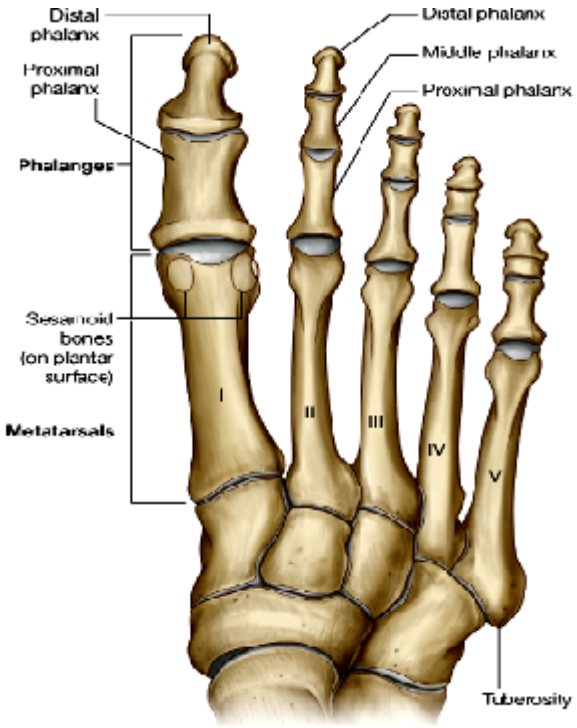


***Figure (2):*** Metatarsals and phalanges. Dorsal view ***(Drake et al, 2004).***

## II. Joints

### - Ankle joint

The ankle joint is synovial in type and involves the talus of the foot and the tibia and fibula of the leg (Fig. 3). It mainly allows hinge-like dorsiflexion and plantar flexion of the foot on the leg. It is also stabilized by medial (deltoid) and lateral ligaments ***(Drake et al, 2004).***