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Research Article

**Study the effect of Zinc/or Vit.D₃ on Percentage of
Healing of Diabetic Foot Ulcer in Iraqi Patients**

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ABSTRACT

To compare the effect of zinc and vit.D₃ on fructosamine level, percentage of healing, and lipid profile in diabetic patient who suffered from diabetic foot ulcer. This study is carried out on 45 diabetic patients suffered from diabetic foot ulcer(s) and 12 healthy subjects. Patients were divided into three groups and assigned for treatment with zinc gluconate (15) patients, vit.D₃ (15) patients and placebo group (15) patients for 4 weeks. We observed fructosamine level, lipid profile and healing percentage before and after 4 weeks of treatment. There is significantly decrease in fructosamine level in medication treated group after 4 weeks of treatment. There is no significant changing in High density lipoprotein, and Low density lipoprote.

Keywords: diabetic foot ulcer, fructosamine, percentage of healing, zinc, vit.D₃.

INTRODUCTION

Diabetes is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, and blood vessels¹. Because various metabolic and nutritional consequences in diabetes mellitus (DM), diabetic patients prone to suffer from nutritional deficiencies e.g. vit.D, vit.B₁₂, Chromium and others². Also, DM patients have reduced antioxidant capacity, and this may play a role in the development of complications³. Foot complications are among the most serious and costly complications of DM⁴. Diabetic foot ulcers (DFU) are sores or wounds on the feet that occur in people with diabetes. If untreated, this foot may need amputation. So preventing is very important⁵. Foot ulcers and their complications are an important cause of morbidity and mortality in patients with DM. About 50% of patients undergoing non-traumatic lower limb amputations have diabetes⁶. Several factors are implicated to DFU and at the end amputation are summarized in fig.1⁷. DFU have a major impact on the patient as well as on the health care system. These ulcers tend to heal slowly, need intensive care and healing can

be complicated by infection and gangrene, leading to long term in hospital treatment and \or amputation⁸. In recent decades, the knowledge on DFU has clearly increased, with a rise in the number of scientific publications and the production of guidelines on prevention and management⁹. In present study, we sought to clarify the effect of micronutrient, zinc gluconate, and vit.D₃, on glycemic control and percentage of healing of DFU.

MATERIALS AND METHODS

Patient Selection

Forty-five diabetic patients with foot ulcers (22 male, 23 female) were participated in this study, mean age 54.52±2.52 years and mean duration of diabetes 13.82±1.87 years. All the patients were present with neuropathic ulcers; some patients were with one ulcer and some with multi. All the patients were having neuropathic ulcer(s) and all of them were treated with standard methods, i.e. debridement, local antiseptic, immobilization of the foot, and antibiotics if necessary. They assigned to receive either zinc or vit.D₃ or placebo. The subjects were recruited from Al-Basrah General Hospital/outpatient clinic and Specialized Center for Endocrinology and Diabetes\Baghdad, Al-Rusafa. Their body mass index (BMI) is around 26.

All the patients treated for 4 weeks and their ulcer(s) is/are classified according Wagner Classification¹⁰. Wagner 0, 1 and 2 were included in this study and Wagner 3, 4 and 5 were excluded. An ethical approval was obtained from Ethical Committee of Baghdad University.

METHOD

Blood sample was taken before and after completing the study to analyze fructosamine, low density lipoprotein (LDL) and high density lipoprotein (HDL). All the patients were orally administered with either zinc gluconate 50 mg once daily after meal, vit.D₃ 1000IU twice daily after meal or placebo. After 4weeks of treatment the changes were determined. Fructosamine is analyzed by colorimetric method (Fortress diagnostics, UK), LDL-c and HDL-c are both determined by enzymatic method (Human, Germany). The ulcer areas are measured pre and post the study manually (cm) and the reduction in ulcer area is calculated by specific formula as shown below.

Statistical Analysis

Data are expressed as means $\pm$ SE. Statistics were performed using Windows Excel 2007. Differences from baseline were assessed by the paired Student's *t* test. A P-value of <0.05 was considered significant.

RESULTS

Patients

Of 45 patients presented to treatment, 15 in zinc group, 15 in vit.D₃ group and 15 in the placebo group. There were no apparent differences between the three groups with respect to demographic data. (Table1).

Fructosamine

Changes from baseline to the end of treatment are summarized in Table 2. Fructosamine was significantly reduced in zinc and vit.D₃ groups, while non-significant effect in placebo group.

Lipid Profile

All treatment groups show non-significant reducing in LDL-c and HDL-c but there is a percent of decrement in LDL-c and increment in HDL-c. These data summarized in Table 2.

Percentage of healing

The percentage reduction in healing of ulcer from the time of the first measurement until the current one can be calculated as following formula: ¹¹

$$(SAI - SAC) / SAI = \dots\dots\dots \% \text{ reduction}$$

*SAI= surface area (L*W) on admission,

SAC= surface area currently

The percentage of healing for three groups is summarized in Table 3.

DISCUSSION

Foot complications of DM present a major problem for clinicians as, at any time, 5% of the diabetic population will have a foot ulcer. This is a significant public health problem in its self, because the treatment and the rehabilitation of patient with foot lesions are extremely demanding on the health care budget ¹². Zinc is identified as a major trace element in the wound-healing process because of its involvement in many different cellular processes ¹³. Also, zinc plays a central role in the proliferation of inflammatory cells and modulates cutaneous inflammation ¹⁴. In addition, vit.D has been shown to play an important role in the disorders of glucose and insulin metabolism. Vit.D supplementation has been suggested to have a role in improving and even preventing type-1 DM ¹⁵. In the skin, vit.D binds to its hormone receptor (VDR), increasing the secretion of cathelicidin. The importance of vit.D and cathelicidin during wound healing turns vit.D an attractive pharmacological target for the treatment of these situations¹⁶. In present study, vit.D₃ and zinc were administered to separate groups to evaluate their effectiveness in accelerating healing process in DFU in diabetic patient in compare with placebo administering group. The present study reported that zinc and vit.D₃ have no significant effect on serum, LDL-c and HDL-c levels, the small sample size and limited duration may lack some of data and cause some of the conclusions to be drawn. In spite of non-significant effect on LDL-c and HDL-c in present study, some researches shown significant effects^{17,18}. The significant effect of both zinc and vit.D₃ on percentage of healing is observed in this study. Zinc is a trace mineral that is a component of many enzymes, including DNA and RNA polymerases, and is required for protein synthesis, DNA synthesis, mitosis, and cell proliferation. Approximately 300 enzymes need zinc for proper functioning; many of these zinc-dependent processes, such as collagen synthesis and cell division, are required for wound healing ¹⁹. The homeostasis of zinc in diabetes is hypozincemia which may be the result of hyperzincuria or decreased gastrointestinal absorption of Zinc or both ²⁰. It has been found that Zinc enhance the effectiveness of insulin in vitro, and it has been postulated that zinc deficiency may aggravate insulin resistance in non-insulin dependent diabetes mellitus (NIDDM) and Zinc replacement could improve insulin sensitivity in NIDDM, as suggested ²¹. Not only Zinc can effect on DM in several ways, but also vit.D decrease insulin resistance and increase insulin secretion in

type II DM by modulation of the immune and inflammatory process²². Vitamin D deficiency has been shown to alter insulin synthesis and secretion in both humans and animal models. It has been reported that vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion and

type 2 diabetes mellitus. Vitamin D replenishment improves glycemia and insulin secretion in patients with type 2 diabetes with established hypovitaminosis D, thereby suggesting a role for vitamin D in the pathogenesis of type II diabetes mellitus²³.

Table 1: Patient characteristic at base line

Characteristic	Zinc	Vit.D ₃	Placebo
n = 45	15	15	15
Age; years	51.26±2.55	56.6±3.21	55.71±1.81
•BMI	26.88±0.89	26.66±1.05	26.55±0.91
Duration of DM; years	12.86±1.91	14.26±1.86	14.35±1.85

•BMI= body mass index, which is calculated according to the following formula:
BMI= weight (kilogram)/height² (meter)

Table 2: Changes from baseline and after 4weeks in fructosamine, HDL-c and LDL-c

Variable\time point	Zinc	Vit.D ₃	Placebo
Fructosamine (µg/ml)			
Baseline	652.8± 102.18	666.5± 114.3	544.13± 82.7
After 4 weeks	211.2± 30.19**	401.2± 68.28*	610.91± 130.6
% of change	-67 %	-39 %	12 %
HDL-c (mg/dl)			
Baseline	34.27± 1.22	37.3± 2.65	38.38± 2.77
After 4 weeks	36.53± 1.52	41.63± 2.12	35.76± 2.59
% of change	6.6 %	11.6 %	-6.8 %
LDL-c (mg/dl)			
Baseline	166.1± 6.73	147.3± 9.5	105.35± 9.13
After 4 weeks	147.1±6.93	138.9± 8.94	116.91± 9.64
% of change	-11.4 %	-5.7 %	10.9 %

Data are given as mean ± SE for baseline and end of study values;

* significantly different when compared to pre-treatment level within the same group ($P<0.05$); ** highly significant difference when compared to pre treatment within the same group ($p<0.01$)

Table 3: Percentage of ulcer reduction after 4 weeks of beginning treatment

Group Parameter	Zinc	Vit.D ₃	Placebo
Percentage of reduction in ulcer size	73.83± 6.08**	71.86± 4.79**	32.06± 4.28

Data are given as mean ±SE; ** highly significant difference compared to placebo at the end of treatment ($p<0.01$)

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CONCLUSION

There is a good effect of both zinc gluconate and vit.D₃ on healing of DFU and in improving glycemic and lipid profile control (if the period of treatment is longer) when used with insulin or oral hypoglycemic agents.

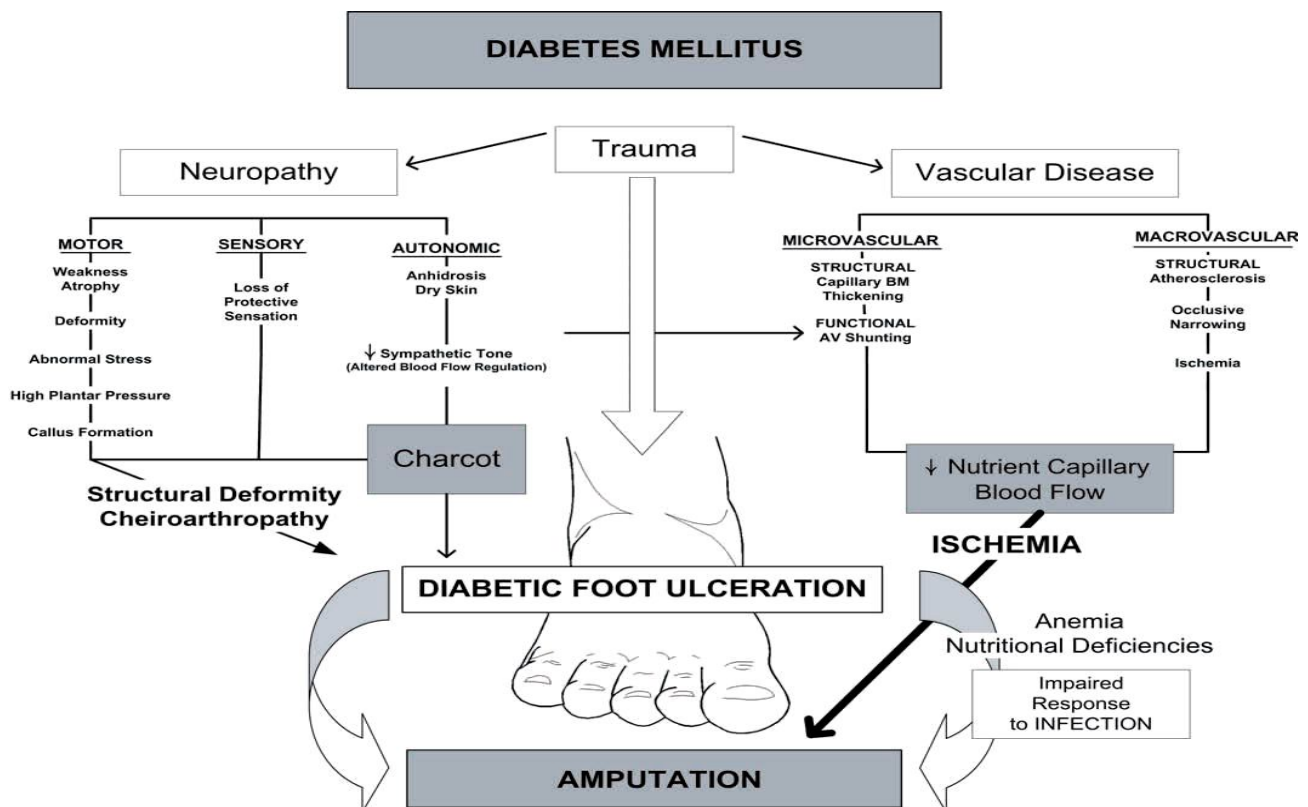


Fig. 1: Diabetes mellitus is responsible for a variety of foot pathologies contributing to the complications of ulceration and amputation. Multiple pathologies may be implicated, from vascular disease to neuropathy to mechanical trauma.⁷

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