

Original article

## Hypomagnesemia: A Significant Risk for Diabetic Foot Ulcer in Diabetic Sudanese Patients

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### Abstract

**Background:** Diabetic foot ulcers (DFU) is one of the significant complications of diabetes mellitus, as it might lead to limb amputations which results in a major medical and economic consequences for both patients and their families. Magnesium ( $Mg^{2+}$ ) is a cofactor in the glucose-transporting mechanism. It is involved in the optimal insulin secretion and/or action.

**Aim:** The aim of this study is to assess the relationship between the hypomagnesemia and the risk of DFU in Sudanese diabetic patients.

#### **Method:**

A cross sectional study was conducted in 117 subjects, out of which; 54 are diabetic patients with DFU as cases and 63 are diabetic patients without foot ulcers as controls. Serum Magnesium levels were measured for both groups using Spectrophotometer

#### **Result**

The results of this study showed that 64.8% of the DFU patients were males with significant gender difference between DFU (cases) and DM (controls) ( $P = 0.032$ ). The highest frequency of the cases and controls (92.6% and 87.3% respectively) are at age  $\geq 45$  years with no significant difference between the two groups ( $P = 0.24$ ).

Serum Magnesium level was measured for both cases and controls. The study revealed that serum hypomagnesemia was reported with high frequency (87%) among DFU patients, with a high significant association with the diabetic foot ulcer susceptibility (DFU) compared to (DM) controls ( $P = 0.001$ ).

Highest prevalence of hypomagnesemia among cases (85%), who have the diabetes for five to fifteen years was observed compared to their counterpart controls, with an extremely statistical significance between the two groups ( $P = 0.0001$ ). This indicates an exponential decrease of magnesium level with an increase of disease duration.

Neuropathy; not only represent the highest frequency of the diabetic complication among the DFU patients (37%), it strongly associated with a five folds increased risk to DFU (OR=5.5). Retinopathy was observed in both DFU and DM patients 29.6% and 38% respectively.

**Conclusion:** This study proposed that hypomagnesemia is a significant risk factor to develop diabetic foot ulceration among diabetic patients. Magnesium level was strictly decreased with the increase of diabetes duration.

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### Introduction

The diabetic foot ulcer (DFU) is one of the diabetes complications. It is associated with a serious morbidity and

mortality among large scale of the affected patients (Josephine and Mark 2013). In Sudan, DFU lead to an

increased lower limb amputation among diabetic patients and accounted for 10% of all complications reported from private clinics in Khartoum State, (Balla *et al.*, 2013).

The etiology of diabetic complications “including DFU” usually involved many contributors, on the top of the risk factors is the poor glycemic control (Bakri *et al.*, 2012). Other complications of diabetes are neuropathy, retinopathy and nephropathy (Josephine and Mark, 2013). The neuropathy leads to nerve damage which is considered as a predisposing factor to ulceration and amputation, resulting in the loss of sensation and unhealed wounds (Alavi *et al.*, 2014).

Magnesium (Mg) is one of the trace elements involved in a wide variety of cellular processes critical to glucose metabolism. It acts as a cofactor in the glucose-transporting mechanism of the cell membrane, which is required for optimal insulin secretion and/or action (Paolisso *et al.*, 1992, Fawcett *et al.*, 1999, Nils-Erik *et al.*, 2000, Chetanet *et al.*, 2002, Sales *et al.*, 2006, Dharam *et al.*, 2010, Goyal *et al.*, 2014). It is well documented that if un controlled hyperglycemia is frequent among diabetic patients; it is possibly lead to the damage of the renal tubules, thereby the kidneys lose their ability to retain magnesium (Olugbenga, *et al.*, 2004). Magnesium is also involved in angiogenesis. The deficiency of Mg also promotes endothelial cell dysfunction and inflammation and impairs angiogenesis (Jeanette *et al.*, 2004) and contribute to the development of diabetic complications (Grafton and Baxter, 1992). In this study we aimed to assess the relationship between the hypomagnesemia and the risk of diabetic foot ulcers (DFU) in Sudanese diabetic patients.

## Methods

Across sectional study was carried out on Sudanese diabetic foot ulcers patients resident in Khartoum State. 117 Hospital-based random samples were collected. 54 with diabetic foot ulcer (DFU) were selected as case group and 63 diabetics (DM) without foot ulcer as control group. Three ml of blood sample were collected in plain

containers. The demographic data of all subjects were obtained using a predesigned questionnaire. Verbal consent was obtained from all participants after we explained the purpose of this study. Hypomagnesaemia was defined as a serum Mg concentration = 1.6mg\dl.

Serum magnesium measurement:

## Principle

Magnesium forms colored complex when react with magsulfonate in alkaline solution. The intensity of the color is proportional to the magnesium concentration in the sample.

## Procedure

Magnesium concentration was measured using Biosystem kit. The procedure according to the manufacture instruction as follows: 1.0 ml from (Reagent) R was added to 3 test tubes, then 10 µL from STD (magnesium Cal) was added to the first test tube and 10 µL from serum was added to the second one and the third test tube was used as blank.

The contents of each tube were mixed well, incubated for 5 minutes at room temperature, then read in Jenway 6305 Spectrophotometer at 540 nm against the blank.

## Calculation

$$\text{Conc. of magnesium (mg/dl)} = \frac{\text{Abs of sample} \times \text{Conc. of STD (mg/dl)}}{\text{Abs of STD}}$$

Abs: Absorption

STD: Standard (Magnesium Cal)

## Statistical analysis

All data were analyzed using SPSS version 16. Statistical significance was determined at  $p \leq 0.05$ .

## Results

The result of this study was demonstrated in Table 1 below. The analysis revealed that more than two third of the diabetic foot ulcer (DFU) are males, with significant gender difference between cases and controls ( $p\text{-value}=0.032$ ).

The highest frequency of both cases and controls are at age  $\geq 45$  years (92.6% and 87.3%) with no significant difference between the two groups (p-value =0.24).

The analysis also showed that hypomagnesemia was not only observed with the highest frequency (87%) among DFU patients, but the association between the low magnesium level and the diabetic foot ulcer predisposition (DFU) as compared to (DM) controls was significant (p-value 0.001), with 3 folds increased risk of DFU (OR=3.36). This indicates an important role of the decreased magnesium level in the development of foot ulcer among diabetics.

High prevalence of hypomagnesemia (85 %) among cases who have the diabetes for five to fifteen years was reported, with a high significant association between the hypomagnesemia and duration of diabetes in case group (p-value=0.0001). However, a non-negligible percentage of hypomagnesemia (66.7%) was also observed among diabetics (DM).

Neuropathy represent the highest frequency (37%) of diabetes complications among the DFU patients. It is strongly associated with DFU (p-value =0.0006) and lead to an up to about six folds increased risk of DFU (OR=5.5).

Retinopathy was observed in both DFU and DM patients (29.6% and 38% respectively) with no significant difference between the two groups (p-value =0.43).

Hypertension was observed with insignificant frequency among DFU, whereas none of the DFU patients develop heart disease.

## Discussion

The changes in the lifestyle: eating full fat foods, smoking, sedentary life and drinking alcohol are expected to deteriorate the situation of DM and the accompanied complications in developing countries (Abdulrahman,1998) including Sudan (Ahmed and Ahmed, 2000).

Diabetic foot ulcer (DFU) in Sudan was considered as one of the serious complications of diabetes, it accounted

**Table 1:** A comparison between the diabetic foot ulcer (DFU) (cases) and diabetic patients (DM) (controls)

	Case (DFU)= 54	Control (DM)=63	p-value, Odds ratio
<b>Gender</b>			
Males	64.8%	49.2%	P=0.032 OR=1.9
Females	35.2%	50.8%	
<b>Age</b>			
35-45	7.4%	12.7%	P=0.24
More than 45	92.6%	87.3%	
<b>Mg level</b>			
Normal Mg level	13%	33.3%	P=0.001 OR=3.36
Hypomagnesemia	87%	66.7%	
<b>Duration of diabetes: &lt;5 years 5-15years</b>			
Normal Mg level	5%	7.5%	P=0.0001 OR=3.34
Hypomagnesemia	2.5%	85%	
<b>Other diseases</b>			
Neuropathy	37.0%	9.5%	P=0.0006 OR=5.58
Neuropathy+ Retinopathy	18.5%	4.8%	
Neuropathy+ Hypertension	0.0%	3.2%	
Neuropathy+ Retinopathy+ Hypertension	0.0%	4.8%	
Retinopathy	29.6%	38.1%	P=0.43
Retinopathy+ Hypertension	7.4%	4.8%	
Heart disease	0.0%	0.0%	
Hypertension	11.1%	22.2%	

for 10% and 48% of DM complications (Ballaet *et al.*, 2013, Ammaret *et al.*, 2016) respectively.

Magnesium was known to play an important role in insulin secretion and/or action (Nils-Erik *et al.*, 2000, Chetanet *et al.*, 2002, Dharam *et al.*, 2010, Goyal *et al.*, 2014).

In this study we aimed to assess the relationship between the hypomagnesemia and the risk of diabetic foot ulcers (DFU) in Sudanese diabetic patients.

A strong association was detected between the low magnesium level and diabetic foot ulcers as compared to DM controls (p-value =0.001). This result agreed the results of the other studies (Kevin *et al.*, 2009, Sakiretal., 2013) and it could be explained by the implications of low magnesium level in modulating endothelium function and impaired angiogenesis (Jeanette *et al.*, 2004). Although the hypomagnesemia results in a three times increased risk of developing DFU (OR=3.36), however, a remarkable percentage of hypoglycemia (66.7%) was also observed among diabetics (DM) which is in agreement of previous finding (Rodríguez-Morán and Guerrero-Romero, 2011, Dasgupta *et al.*, 2012, Seedahmed and Ahmed, 2013). This might be due to hyperglycemia in both DFU and DM patients which increase the urinary loss of magnesium. This study also revealed that the hypomagnesemia was strictly associated with the increased duration of DM (p-value=0.0001), which is consistent with (Augusta *et al.*, 2006).

The neuropathy as one of the DM complication was known to be one of the causes of the impaired peripheral nerve function that leads to the loss of sensation (Alavi *et al.*, 2014, Chen *et al.*, 2016), this in turns claimed the neuropathy as a contributor to diabetic foot ulcer risk. This fact explains our result that showed that the neuropathy was associated with about six times increased risk of DFU susceptibility (OR=5.58), this could be attributed to the association of low serum magnesium levels with DFU reported by Sakir *et al.*, 2013.

We also found that, males with DFU were more affected by ulceration than females with p value 0.032 which is in agreement with the finding of the previous studies (Augusta *et al.*, 2006). Although in this study we did not get information about the smoking habit or alcohol consumption, however males increased risk of DFU could be attributed to

smoking cigarette or tobacco which was known to increase the risk of diabetic foot predisposition to more than 2 folds in a study conducted in patients from Sudan by (Ammar *et al.*, 2016).

In a summary, the strong association of hypomagnesemia with DFU and with the increased duration of DM and the significant association of neuropathy with DFU; in our opinion; all these collectively could be strictly explained by the circuit that is normally ruled out by the maintained magnesium level: In DM patients the frequent hyperglycemia with increasing duration of diabetes results in a continued loss of Mg in the urine or as a result of renal tubules dysfunction, this condition impairs proper insulin secretion or action, which in turns leads to more hyperglycemia there by more loss of Mg and this circle continues. Such situation can potentiate the risk of diabetic complications.

### Conclusion

Hypomagnesemia is a significant risk factor to developing diabetic foot ulceration among Sudanese diabetic patients. Magnesium level was strictly decrease with the increase of diabetes duration.

### Recommendation

- A cost-effective regime must be conducted which involves a routine measurement of Magnesium level for both diabetic patients with or without foot ulcers.
- Modification of lifestyle to maintain glucose and  $Mg^{+2}$  at normal levels for both healthy and diabetic patients.

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