Subject Area:

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Renal function and diabetic foot ulcer

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Abstract

Introduction
Diabetic nephropathy has been identified as an essential risk factor for foot ulceration and amputation. Renal failure has been reported to independently predict the risk of nonhealing ischemic and neuroischemic foot lesions and major amputation.

Objective
In this study, we aimed at assessing the renal function of diabetic foot infected patients.

Patients and methods
We included 120 patients with type 2 diabetes mellitus, patients participated from the medical and surgical unit, Shebin El Kom Teaching Hospital, Egypt. They were divided into two main group; group 1 included 80 patients with an active diabetic foot ulcer (DFU) and group 2 included 40 patients without an active or past history of DFU. Also, group 1 was subdivided into two groups; 40 patients were included in group A, who had antibiotic therapy with a low profile of renal toxicity (ceftriaxone, clindamycin, and ciprofloxacin) and 40 patients were included in group B who had antibiotic therapy with a high profile of renal toxicity (imipenem, aminoglycosides, and vancomycin).

Results
Patients with DFU had significant increase in neuropathy, history of lower limb amputation, and cerebrovascular accident. Also, patients with DFU had increased fasting blood glucose, 2 h postprandial glucose, glycated hemoglobin. Moreover, patients with DFU had increased serum creatinine and decreased estimated glomerular filtration rate. Also, serum creatinine was high in patients with DFU who received antibiotics with higher nephrotoxicity.

Conclusion
There was a strong association between the degree of renal impairment and DFU. Renal function decreased after antibiotherapy. In patients receiving antibiotics with higher nephrotoxicity, its decline was steeper. Further study is required to identify factors affecting renal function in patients with a DFU.

Keywords: Amputation, diabetic foot, renal function

INTRODUCTION
Diabetes type 2 is a globally common chronic disease, with its prevalence and vascular complications taking a toll on the health system [1]. Worldwide, the commonly occurring complication of diabetes is the diabetic foot with subsequent infection and is the direct cause of morbidity and premature mortality in diabetics [2]. Owing to neuropathy and potential coexisting vascular disease, about 25% of all diabetic individuals during their lifetime are affected, following a trauma that often goes unnoticed, ulceration occurs, and diabetic foot process is initiated [3]. It is complicated by ulceration and result in lower limb amputation if it is not promptly and comprehensively assessed [4].

Diabetic nephropathy has been identified as an essential risk factor for foot ulceration and amputation [5]. Additionally, dialysis treatment has been reported as an independent risk factor in diabetic patients with chronic kidney disease [6].

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About 20% of diabetic patients develop foot ulcers during early initiation of dialysis [7], and the amputation rate is 4% every year in dialysis therapy [8]. Moreover, renal failure has been reported to independently predict the risk of nonhealing ischemic and neuroischemic foot lesions and major amputations [9]. Uremia has an adverse effect on ulcer healing. With nonuremic patients having a 2.45 increasing probability of primary healing of the ulcer [10]. Additionally, end-stage renal disease (ESRD) has a stronger adverse effect in diabetic patients with peripheral arterial disease (PAD) than in those without this complication [11]. The antibiotic treatment (antibiotherapy) plays a strong role in treatment strategy for infections. Wounds without infection of soft tissue or bone tissue do not require antibiotic treatment. Empiric treatment, is covering gram-positive cocci, is used for the treatment of mild and moderate infection. When antibiotics are needed for severe infections, it must be covering gram-negative aerobes and obligate anaerobes [12].

Antibiotics used mainly against gram-positive organisms are amoxicillin, co-amoxiclav, fluoxacillin, erythromycin, clarithromycin, fucidin, doxycycline, rifampicin, clindamycin, vancomycin, linezolid, trimethoprim, tigecycline. Antibiotics used mainly against gram-negative organisms are ciprofloxacin, septrim, ceftriaxone, ceftazidime, piperacillin/tazobactam, ticarcillin/clavulanic acid, imipenem with cilastin, meropenem, ertapenem, tigecycline, and aminoglycosides. Antibiotics used against anaerobic organism are metronidazole, clindamycin, meropenem, piperacillin/tazobactam, and entrapenem [13].

**Patients and methods**

This study included 120 patients with type 2 diabetes mellitus (DM). Patients participated from the medical and surgical unit, Shebin El Kom Teaching Hospital, Egypt.

They were divided into two main group; group 1 included 80 patients with an active diabetic foot ulcer (DFU) and group 2 involved 40 patients without a history of an active or past DFU. Also, group 1 was subdivided into two groups; which included 40 patients in group A who received antibiotics with a low profile of renal toxicities (ciprofloxacin, ceftriaxone, and clindamycin) and included 40 patients in group B who received antibiotics with a high profile of renal toxicity (aminoglycosides, vancomycin, and imipenem).

Exclusion criteria; included patients who were with the ESRD; patients with hemodialysis, and patients with lower knee amputation.

Inclusion criteria; included type 2 DM patients, age more than 35 years, diabetic foot diagnosis was established on the basis of clinical criteria; current foot ulcer, history of nontraumatic ulcer, and all ulcer and limb threatening lesions that occur on or below the malleoli [14].

Stages of foot ulceration were recorded according to the Wagner criteria:

1. Grade 0: ulcers are preulcerative or postulcerative lesions.
2. Grade 1: ulcers are superficial, involving partial or full skin thickness.
3. Grade 2: ulcer are deeper penetrating down to ligaments and joint capsule.
4. Grade 3: are deep lesions with abscesses or osteomyelitis.
5. Grade 4: forefoot gangrene.
6. Grade 5: whole foot gangrene [15].

Full clinical history of hypertension, ischemic heart disease, and cerebrovascular accident was analyzed. Comprehensive clinical examination was carried out for BMI, blood pressure, examination of peripheral pulse, and presence of neuropathy. Evidence of PAD defined as a history of surgical revascularization of a peripheral artery or angiography confirming PAD [16]. The absence of two or more foot pulse on palpation or an ankle-brachial index less than 0.9 [17].

Albuminuria was determined by nephelometry in the first morning through urine samples, and urine albumin–creatinine ratio was done. Serum creatinine, lipid profile, glycated hemoglobin (HbA1c) was measured. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease equation.

Statistical analysis

Statistical analysis was performed using SPSS, version 13.0 (Corporate headquarters 1 New Orchard Road Armonk, New York 10504-1722 United States US: 914-499-1900). Data were analyzed using $\chi^2$ test and Student’s $t$ test, $P$ value less than 0.05 was accepted as significant.

**Results**

Table 1 shows demographic and anthropometric characteristics of the study groups. Group 1 included 80 patients with an active foot ulcer, mean age 57.5 ± 7.2 years that was significantly higher than the mean age of group 2, which was 43.2 ± 7.5 years. No significant difference was found between both the groups with respect to BMI and treatment of oral hypoglycemics.

Table 2 shows diabetic complications of the study population, there was the statistically significant difference between both the groups with respect to the presence of peripheral neuropathy, cerebrovascular accidents, and history of lower limb amputation. In contrast, there were no
statistically significant differences between both the groups with respect to the presence of retinopathy, the presence of ischemic heart disease, mean ankle-brachial index, the presence of dorsalis pedis and posterior tibial pulsation, and performance of revascularization or performance of angiography.

Table 3 shows laboratory investigation of the study groups. There were high significant differences between both the groups with respect to fasting blood glucose, 2 h postprandial glucose, HbA1c. In contrast, there was no significant difference between both the groups with respect to lipid profile (serum cholesterol, serum low-density lipoprotein, serum high-density lipoprotein, serum triglycerides).

Table 4 shows comparison of renal function and urine albumin/creatinine ratio of the study groups. There was a high significant increase in serum creatinine (2.3 ± 0.93 vs. 1.5 ± 0.73) and no significant difference in albumin/creatinine ratio in urine (235.5 ± 274.5 vs. 219.3 ± 112.3) in group 1 versus group 2, and a considerable decrease was seen in eGFR in group 1 versus group 2 (40.3 ± 24.5 vs. 62.4 ± 23.4) (P < 0.001).

Table 5 shows renal function before and after antibiotics in group A (low-risk regimen), there was no statistically significant difference in renal function after treatment (40.6 ± 23.1 vs. 39.5 ± 15.1) (P > 0.05). In contrast, group B (high-risk regimen) there was a significant decrease in renal function after the treatment (40.0 ± 25.7 vs. 34.6 ± 17.4) (P < 0.05).

**Discussion**

Disability in patients with DM is mainly caused by foot ulcers and infections [18]. Foot ulcers develop in about 15% of people with diabetes [19]. Infection are frequently in form of DFUs and take a long time to heal.

Our study showed that patients with DFU had high significant difference with respect to the history of lower limb amputations, cerebrovascular accidents, and peripheral neuropathy compared with type 2 DM without DFU. In agreement with our results, Abd El basset et al. [20] reported an association between history of DFU and peripheral neuropathy, history of lower limb amputation, and cerebrovascular accident.

Our study showed that patients with DFU had a high significant difference with respect to fasting blood glucose, 2 h postprandial blood glucose, HbA1c. Similarly, Wolf et al. [21], concluded that type 2 DM with diabetics foot syndrome were significantly higher HbA1c and had a longer duration of diabetes compared with type 2 DM without diabetics foot syndrome.

Our study is finding that significant association between renal function and DFUs, patients with foot ulcers showed significantly higher serum creatinine and substantially lower mean eGFR compared without ulcer, similar to Abd El Basset and colleagues.

Also, our study showed that nonsignificant increase in the prevalence of foot ulcer with increasing degree of microalbuminuria. WolF and colleague reported that DFU occurs significantly more often in patients with

### Table 2: Associated diabetic complications of the study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=80)</td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[n (%)]</td>
<td>[n (%)]</td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>27 (33.8)</td>
<td>9 (22.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>50 (62.5)</td>
<td>11 (27.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IHD</td>
<td>28 (35)</td>
<td>12 (30)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CVA</td>
<td>8 (10)</td>
<td>2 (5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ABI</td>
<td>1.02±0.25</td>
<td>1.07±0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>History of LL amputation</td>
<td>19 (23.8)</td>
<td>0.0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dorsalis pedis pulsation</td>
<td>38 (47.5)</td>
<td>21 (52.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Posttibial pulsation</td>
<td>60 (75)</td>
<td>31 (77.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Revascularization performance</td>
<td>12 (15)</td>
<td>4 (10)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Angiography performance</td>
<td>16 (20)</td>
<td>7 (17.5)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ABI, ankle-brachial index; CVA, cerebrovascular accident; IHD, ischemic heart disease; LL, lower limb.

### Table 3: Laboratory investigation of the study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=80)</td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>230±60.4</td>
<td>185±50.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 h postprandial glucose (mg/dl)</td>
<td>305±84.3</td>
<td>230±60.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.8±1.2</td>
<td>7.4±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>240±55.3</td>
<td>230±60</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum LDL (mg/dl)</td>
<td>150.2±28.4</td>
<td>143.3±31.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum HDL (mg/dl)</td>
<td>40.7±11.6</td>
<td>42.3±13.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)</td>
<td>215.4±50.7</td>
<td>209.3±60.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

### Table 4: Comparison of renal function and urine albumin/creatinine ratio of the study groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=80)</td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.3±0.93</td>
<td>1.5±0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>40.3±24.5</td>
<td>62.4±23.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio</td>
<td>235.5±274.5</td>
<td>219.3±112.3</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. eGFR, estimated glomerular filtration rate.

### Table 5: Renal function before and after antibiotics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before treatment eGFR</th>
<th>After treatment eGFR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (low-risk regimen)</td>
<td>40.6±23.1</td>
<td>39.5±15.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Group B (high-risk regimen)</td>
<td>40.0±25.7</td>
<td>34.6±17.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. eGFR, estimated glomerular filtration rate.
nephropathy, macroalbuminuria, ESRD, but not in those with microalbuminuria. People with diabetes and those with ESRD share three risk factors whose interaction undoubtedly increase their risk of developing foot ulceration and amputation and neuropathy. PAD increase susceptibility to infection with impaired wound healing.

In our study, GFR decreased after antibiotic therapy in diabetic patients mainly because of abnormal renal function [22]. Lepantalo et al. believed that the essential factor for DFU is a loss of renal function [23]. Disturbance of glucose metabolism and production of glycogen is caused by damaging insulin binding to receptors that cause tissue-insulin resistance, particularly in skeletal muscles. It is also caused by the level of elevation of parathyroid hormone and uremic toxins accumulation in patients with chronic renal failure [24].

In our study, in patients with antibiotics treatment, we found a decrease in renal function. In higher renal toxicity, treatment with antibiotics significantly decreased renal function. Although, regardless of nature and mechanism, the toxicity of antibiotics, depends on the dose, concentration, duration, and another underlying disease. In diabetic patients, as renal dysfunction is more liable, antibiotic therapy should be carefully monitored in these patients because antibiotics can accelerate renal dysfunction [25].

Conclusion

There was a strong association between the degree of renal impairment and DFU. Following antibiotic therapy, we observed that the renal function decreased. Antibiotics with higher nephrotoxicity in diabetic patients showed steep decline in renal function. Further study is required to identify factors affecting renal function in patients with a DFU.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

23. Lepantalo M, Fiengo L, Biancari F. Peripheral arterial disease in